Chapter 5

# Comorbid Conditions in Child and Adolescent Patients Diagnosed with Attention Deficit/Hyperactivity Disorder

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Additional information is available at the end of the chapter

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**Abstract**

Attention deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders. The worldwide prevalence of ADHD in children has been reported at 4-7%. Numerous population- and clinical-based studies have reported that more than half of cases of ADHD have at least one psychiatric comorbidity. The presence of psychiatric comorbidities complicates the diagnosis, treatment, and prognosis of ADHD; thus, diagnosis of comorbidities is of great importance. Possible comorbidities should therefore be investigated in cases diagnosed with ADHD before treatment planning.

**Keywords:** Attention deficit/hyperactivity disorder, psychiatric comorbidity

## 1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders. This disorder is multifactorial in origin and clinically heterogeneous, leads to socioeconomic burdens, and has undesirable academic and occupational outcomes [1]. The worldwide prevalence of ADHD in children is reported to be 4-7% [2]. Results of long-term studies have revealed that a substantial proportion of individuals suffering from ADHD during childhood continue to exhibit symptoms of ADHD during adolescence and adulthood [2, 3]. Numerous population-based and clinical studies have reported that more than half of

the patients suffering from ADHD have at least one psychiatric comorbidity and that this rate increases with age [4-6].

These comorbidities may be different manifestations of the same disorder or may have different diagnoses while sharing a common disposition. Similarly, ADHD may be an early manifestation of another disorder and may place the individual at risk of developing the same [7].

These comorbid psychiatric conditions are more common in boys than in girls [1, 8-11]. One study conducted in Switzerland reported at least one comorbidity in 87% of the ADHD cases and more than one comorbidity in 67% [4]. Biederman et al. [7] have reported two or more comorbidities in 20% of ADHD patients admitted to clinics. A study from Iran found at least one psychiatric comorbidity in 73% of the childhood and adolescent cases of ADHD [12]. A clinical study from Turkey also documented the presence of at least one comorbid psychiatric disorder in 96% of the children diagnosed with ADHD, assessed according to KSADS-PL [13].

The presence of psychiatric comorbidities complicates the diagnosis, treatment, and prognosis of ADHD, and thus, the diagnosis of comorbidities is of great importance [14]. Possible comorbidities should therefore be investigated in patients diagnosed with ADHD before planning treatment regimens, and the possibility of comorbidities arising during follow-up should be taken into account [13].

## 2. Disruptive behavior disorder

Disruptive behavior disorders (DBD) are the most common comorbidities accompanying ADHD. Individuals with oppositional defiant disorder (ODD) and conduct disorder (CD) share many characteristics. For example, their conduct is socially unacceptable, they cause disruption or distress to others more than to themselves (i.e., they "externalize" their problems), they are more likely to be male, and they find it difficult to learn from experience. ODD and CD are commonly investigated together in most studies to highlight their similarities and differences. Biederman et al. [15] studied the prevalence of comorbidities in children and adolescents with ADHD aged 6-17 years and reported high rates for ODD (46% in children and 33% in adolescents) and CD (25% in children and 42% in adolescents).

One study that investigated the effect of gender on the clinical features of ADHD reported that girls with ADHD are at reduced risk for developing comorbid major depression, conduct disorder, and oppositional defiant disorder compared to boys with ADHD [16]. In clinical practice, disruptive behavior disorders have a poorer prognosis when they are comorbid with ADHD rather than alone and other accompanying comorbid psychiatric disorders. One population-based prospective study in a broad sample reported an increased risk of unipolar depression and bipolar disorder in ADHD, and that the risk was greatest in the group with ADHD and comorbid CD or ODD [17]. ODD is the most common comorbid psychiatric disorder and is associated with an increase in intrafamilial and social problems, irrespective

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of whether or not CD accompanies ODD [18]. Disruptive behavior disorders that are comorbid with ADHD are an important factor in determining the clinical picture. Adolescents diagnosed with DBD and ADHD are at a higher risk of undergoing psychiatric hospitalization at some time in their life [19].

The overlap of ADHD and conduct problems is explained by common genetic and non-shared environmental factors that influence both disorders. Nevertheless, the two disorders appear to be partly distinct, in that additional environmental factors influence the severity of the behavioral problems. It appears that ADHD+CD is a genetically more severe variant of ADHD [20].

One study compared patients with ODD/CD, comorbid ADHD, and those with only ODD/CD. Both the patient subgroups had deficits in visuospatial working memory compared to the control subjects, indicating that children with ODD/CD have deficits in visuospatial working memory that are independent of the comorbid ADHD, and that a deficient working memory may be an underlying factor in the development of ODD/CD [21].

Two subtypes of ODD are associated with ADHD, one that is prodromal to CD and another that is subsyndromal to ADHD and unlikely to progress into CD in the later years. These ODD subtypes have different correlates, courses, and outcomes. In a large, well-characterized, cross-sectional sample of children with ADHD assessed at baseline and 4 years later at midadolescence, Biederman et al. found that the majority of the children with ODD did not have comorbid CD. In contrast, CD was almost always comorbid with ODD. When ODD co-occurred with CD, it preceded the onset of CD by several years. These findings indicate that the two subtypes of ODD within ADHD can be distinguished as either being prodromal to CD or not. The study also found that CD and ODD had similar correlates, and that these were less severe in children suffering from ODD than CD, thus supporting the initial hypothesis that ODD is a subsyndromal form of CD. This notion assumes that both disorders are part of the same disease process in which CD is the more severe form while ODD is the less severe form of the same disorder. Their findings, that CD is almost always comorbid with and precede ODD, are also consistent with the second hypothesis that a subtype of ODD is prodromal to CD. This subtype differs from the other type of ODD in that there is significantly higher risk of familial antisocial disorders, comorbidity with mood and anxiety disorders, earlier age at onset of ODD, higher number of comorbid psychiatric disorders, and greater number of ODD symptoms [22].

One study involving the long-term monitoring of CD and ODD patients identified an increased risk of long-term depression in patients with ODD and comorbid ADHD. The same study also reported that patients with accompanying CD are at risk of developing psychoactive substance use disorders and bipolar disorder in the long term [23]. Increased conflict, impaired communication, and incompatibilities between parents and the child also lead to an increased risk of ODD and CD in adolescents with ADHD [24]. While ODD is a precursor of CD, certain additional risk factors are required for ODD to progress to CD. The clinical features of young people with CD include a predominance in males, low socioeconomic status, and familial aggression [25]. Wilson and Morcotte divided ADHD patients aged between 14 and 18 years into two groups as with or without CD and compared these two groups in terms of success at

school, self-perception, behavior problems, alcohol and substance abuse, and adaptive behaviors. They reported that patients with CD exhibit significantly lower rates of success in school, greater externalizing behaviors and emotional difficulties, and lower adaptive behaviors compared to patients without CD [26].

The response to treatment in patients with ODD and CD comorbid with ADHD may vary, and there is a greater need for integrative therapeutic approaches in these cases. A higher dose of ADHD drugs may be required, apart from combined drug use, particularly atypical antipsychotics. Atypical antipsychotics are very frequently used in patients exhibiting ADHD and disruptive behavior, and studies have mainly focused on risperidone. One meta-analysis published recently reported that among the atypical antipsychotics, risperidone has a positive effect on aggression and behavioral disorders in the 5- to 18-year age-group; however, similar data on other atypical antipsychotics are not available [27]. Another recent study also compared risperidone and placebo in 168 patients aged 6-12 years diagnosed with ADHD+ODD/CD who were prescribed methylphenidate and a parental education program. A reduction in aggression and attacks on peers was observed when risperidone was added, but it was not particularly effective in relieving the symptoms of the behavior disorder [28]. One open study from Turkey suggested that aripiprazole reduce anger and guilt in cases of ADHD+CD [29]. Nondrug therapies are of great importance in the treatment of ODD and CD, and multidimensional therapies are indicated since the basis of these conditions lie in familial dysfunction, societal problems, and disorganized families. Studies have shown that parental education programs, when combined with a behavioral approach, have a positive effect on children with ODD with respect to nonrule governed actions, anger, and negativism. In addition, enrollment in sports programs also has a positive effect on this group of patients [30], and patient participation in other therapeutic approaches increases following an effective drug therapy.

## 3. Learning disorders

Learning disorder (LD) is a common comorbid condition in ADHD. One review of the studies on ADHD/LD comorbidity conducted between 2001 and 2011 reported wide differences in comorbidity rates, and rates of LD comorbidity in patients ranged between 8% and 76%. Greater difficulties in writing, but not in reading or mathematics in particular, were reported by the studies on patients with high comorbidity rates [31-33]. Morgan et al. [34] reported that the type of mathematical learning disorder that is more common in cases with ADHD is predominantly the inattentive type. The median prevalence rate of LD was 45% in another study, indicating that, on an average, one out of every two children with ADHD also have LD [35].

Several studies have investigated the etiology of ADHD+LD comorbidity, and structural and functional neuroimaging studies, and behavioral, genetic, and molecular research has revealed the existence of a complex relationship between these two disorders [36].

ADHD and LD share some common symptoms. For example, an attention deficit may have an adverse effect on a child's concentration and learning process. The inability to concentrate

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on details and making of careless errors also have a negative effect on knowledge acquisition and accurate information gathering. Confusion between alphabets (such as between b and d seen in children with a reading disorder) may also be seen in inattentive children. They may also have difficulties in solving mathematical problems due to their inability to concentrate on details and errors may occur while writing. Thus, children with a learning disorder are reluctant to study because they cannot acquire effective reading, writing or mathematical skills, and similarly, children with ADHD avoid tasks that require uninterrupted attention. As children with a learning disorder have problems transferring information from their short-term memory to their long-term memory and in processing that information, they may forget the information after some time, thus feeling as if they had never acquired it to begin with. Forgetfulness can also be seen in children with ADHD.

Academic difficulties associated with an attention deficit may increase over the course of time in children with ADHD, and this can be confused with LD [37]. Symptoms of an attention deficit in children with ADHD have an adverse impact on the learning processes and lead to the clinical manifestation of learning disorders. If these two disorders are comorbid, then the symptoms may follow a more severe course. Therefore, the presence of LD should be investigated when ADHD is diagnosed, and a differential diagnosis should be performed.

Children with ADHD and LD together are also more resistant to treatment. Comorbid LD must be considered in patients with ADHD who do not show improvement despite treatment. A 6-week randomized, double-blinded, place-controlled study that compared the effectiveness of methylphenidate in ADHD with or without comorbid LD reported that behavior and performance improved with oral methylphenidate in both the groups [38]. The effectiveness of methylphenidate in alleviating the core symptoms of ADHD is clear, but there is insufficient evidence supporting its efficacy in LD alone.

Another study assessed the response to atomoxetine therapy in ADHD and ADHD accompanied by dyslexia and reported a significant improvement in ADHD symptoms and reading scores in both the groups. A correlation analysis performed in the same study showed that improvement in reading was not by itself sufficient to account for the decrease in symptoms of ADHD. Further research is needed to ascertain the potential effects of atomoxetine on reading in children with ADHD+dyslexia or dyslexia alone [39].

Pharmacotherapy alone is insufficient to treat children with ADHD+LD. Psychological therapies can be added to pharmacological treatment, but more research is required to clarify their role in the treatment of ADHD and comorbid learning disability [40]. Special education techniques also need to be used in such cases.

## 4. Intellectual disability

ADHD is a widespread clinical condition in individuals with intellectual disability (ID). One study that investigated psychiatric comorbidities in groups with or without ID reported that the greatest difference between the two groups was in the rate of meeting the diagnostic criteria

for ADHD (ratio = 3.21:1). The same study also reported a correlation between high stability of externalizing behavior problems at age 3 to a diagnosis of ADHD at age 5 in both the groups [41]. Another longitudinal study investigated ADHD in children with or without accompanying ID and monitored these children from the age of 5 till the age of 8 years. ADHD was three or more times prevalent in the ID group compared to typical development across ages 5, 6, 7, and 8 years, and ADHD tended to be diagnosed earlier and was more stable in the ID group [42].

Children with ID exhibit a greater risk for developing ADHD, and the disorder may follow a longer and more persistent course, apart from increasing the risk of developing further psychiatric problems. These findings highlight the need for making available the interventions necessary for early treatment of ADHD in children with ID.

One study on the effectiveness of stimulant drug therapy in children diagnosed with ADHD and ID reported that the symptoms of ADHD could be successfully treated in children with ADHD and ID [43]. A randomized, controlled, double-blind study of children with severe ADHD and ID suggested that methylphenidate is effective in reducing the symptoms of ADHD in these children [44]. Stimulants have a similar effect on improving impulsivity, hyperactivity, and attention deficit in children with IQ ranging between 45 and 75 compared to normal children; however, they may exhibit fewer improvements in learning and memory. Stimulants appear to have a positive effect in preschool children, albeit with more side effects [45]. Reduced appetite, nausea, and irritability are the most common adverse events reported in children with developmental disabilities (DD); clinicians should be aware that, as with stimulants, irritability appears to occur much more commonly in children with DD than in normally developing children. Initial splitting of the dose, starting below the recommended dose, and slowly titrating the dose may prevent or ameliorate these side effects [46].

Only one open-label study has investigated the effectiveness of atomoxetine (ATX) in children with ADHD and ID not accompanied by the autism spectrum disorder (ASD). Atomoxetine appears to be useful in improving ADHD symptoms in individuals with ID. Larger, randomized, controlled, double-blind studies are required to confirm the efficacy of ATX in children with ID without ASD [47].

Clinicians must carefully consider the following when treating cases of ID with ADHD. As patients in this group may have a lower tolerance to side effects, greater care must be taken during dose titration, and drugs must be started at low doses and gradually increased. Antipsychotic agents such as risperidone can lead to an improvement in irritability. Many children with ID may have a micronutrient imbalance that could benefit from an RDA/RDI multivitamin/mineral supplement, especially if appetite has been suppressed by the stimulant [48].

## 5. Depression and anxiety disorder

Prospective studies show that children and adolescents diagnosed with ADHD are also more frequently diagnosed with major depressive disorder (MDD) compared to control subjects

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[49]. Additionally, ADHD is more common in children with major depressive disorder [50]. Studies that have investigated internalizing problems, such as depression and anxiety in the subtypes of ADHD, have shown that internalizing problems are more common in the attention deficit ADHD subtype [51]. CD and ODD seem to appear in early childhood in ADHD, while the symptoms of depression and anxiety appear later [52].

Several studies have been performed to explain the etiology of comorbid ADHD and depression. These studies have shown a genetic overlap between ADHD and depression, and both disorders involve dopamine reward circuit problems and difficulty in emotional regulation. A dysfunctional relationship with parents has also been shown to play a role in the etiology of comorbidities in children with ADHD [51].

Symptoms of depression, such as sleep disorders, difficulty concentrating, and irritability, and symptoms of anxiety disorders, such as sustained anxiety and failure to concentrate, may be confused with ADHD and lead to a misdiagnosis. Depression or anxiety accompanying ADHD make diagnosis difficult and result in greater severity of symptoms [53]. Depression is 2.5 times more frequently diagnosed during adolescence and early adulthood in girls previously diagnosed with ADHD, and the onset of depression is earlier and is more protracted. Depression leads to greater depression-related loss in functionality, increases disposition to suicide, and requires more hospitalization [54]. The adverse effect of comorbid ADHD on the prognosis of depression and the higher incidence of attempted suicide in hyperactive young people make the identification of comorbid depression and ADHD particularly important. It is also important not to overlook the depressive disorder comorbidity in children diagnosed with ADHD as the depressive disorder can increase the severity of attention problems in ADHD [55]. One study showed that the probability of developing comorbid bipolar affective disorder or major depression is higher in patients with ADHD than in patients suffering from major depression alone [56]. One study, intended to determine which children with ADHD subsequently develop depression, showed that ADHD patients with comorbid anxiety and/or disruptive behavior disorders have a higher probability of developing depression [57]. Measures can be taken to avoid the development of depression in ADHD patients who are diagnosed with comorbid anxiety and/or disruptive behavior disorders. While the existence of anxiety in ADHD has an improving effect on DBD, performance anxiety and feelings of inadequacy are thought to be more prominent [58]. Although anxiety reduces the inhibition response in anxiety ADHD and impulsivity, it can worsen work memory test performance [59]. A detailed investigation of the psychiatric symptoms in the family will assist physicians with the diagnosis and treatment of these patients.

Recent familial, genetic, and long-term follow-up studies have demonstrated that ADHD and major depressive disorder share a common familial risk [60]. Comorbidity of ADHD and emotional disorders (such as anxiety) determines the severity of the clinical symptoms and leads to severe social maladaptations.

Since environmental factors make a significant contribution to the development of depression in individuals with ADHD, overcoming these environmental factors and relational problems is an important part of treatment. If the depressive symptoms are mild, treatment starts with assuaging ADHD, and this itself frequently leads to a resolution of the depressive symptoms.

If no improvement in the depressive symptoms is observed, SSRIs may be added. Appropriate dosage and gradual titration are important when using SSRIs.

Depression-related nondrug therapies, particularly cognitive behavioral therapy, may be started along with ADHD drugs in this group. One study on adolescents diagnosed with depression compared the relative effectiveness of three therapeutic approaches, namely, fluoxetine, CBT, and combined treatment, with a placebo. Only combined treatment emerged superior to the placebo in patients with depression alone, but fluoxetine, CBT, and combined treatment were all better than the placebo in adolescents with ADHD and comorbid MDD [61].

The form of treatment that should be undertaken when these disorders are comorbid with ADHD is controversial, and the disorder dominating the general picture should be treated primarily. If there is no doubt regarding the diagnosis of both disorders and the clinical picture is sufficiently severe to require treatment, then such treatments may be started together. Despite a scarcity of well-designed treatment studies in youth with ADHD and comorbid depression, there is increasing preliminary evidence on the role of stimulants, selective serotonergic reuptake inhibitors, bupropion, and atomoxetine in targeting either or both disorders. There is also some indirect evidence on the benefits of combining pharmacological treatments with psychosocial interventions that specifically target relevant environmental factors and functional impairments [62].

In cases of comorbid ADHD and anxiety disorder, therapeutic priority is determined on the basis of the severity of both disorders and the extent of their negative impact on life. If the anxiety is not very severe, then priority must be attached to treating ADHD. In addition, if the patient is amenable to psychotherapy, then this can also be recommended for improving the anxiety disorder in parallel with ADHD treatment. If the anxiety disorder symptoms are very severe, however, SSRIs must be added to the treatment regimen. CBT has been shown to be effective in both adolescents and adults. In addition, psychosocial therapies should be advised in patients with anxiety disorder [30].

## 6. Bipolar affective disorder (BAD)

Comorbidity or merging of ADHD and BAD is not yet fully understood. There are a number of questions concerning the relationship between these two disorders, such as is there symptomatic similarity between ADHD and BAD, is one a precursor of the other, are ADHD and BAD familial subtypes, are there any similarities in terms of comorbidity and course?

The three symptoms sufficient for diagnosing a manic attack in children, namely, distractibility, excessive talking, and hyperactivity, are also compatible with a diagnosis of ADHD, and given these overlapping symptoms, it is possible that BAD may be misdiagnosed as ADHD or vice versa. The rate of ADHD comorbidity in children diagnosed with BAD ranges from 11% to 98% [63], while BAD comorbidity is lower in individuals with ADHD. This variation may be because ADHD is more commonly diagnosed in children rather than BAD. The prevalence of ADHD in children is higher than BAD, and the predictors of bipolarity may not be completely determined in the presence of comorbid ADHD.

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Biederman et al. [63] conducted a 4-year follow-up study and found that the rate of comorbid bipolar disorder increased by an additional 12% at the end of the 4 years; 11% of the children with ADHD had comorbid bipolar disorder at baseline, and these prevalence rates were significantly higher compared to control groups without ADHD. Furthermore, significantly higher rates of additional psychopathology, psychiatric hospitalization, and severely impaired psychosocial functioning were observed in children with ADHD and comorbid BAD, compared to children with ADHD alone both at baseline and at follow-up assessment. The authors also suggested that comorbid ADHD and bipolar disorder do not result from overlapping symptoms.

Co-occurrence of these two disorders is associated with poorer global functioning, greater symptom severity, and additional comorbidity compared to either disorder alone [64].

Available data strongly suggest that the prepubertal onset of BAD is a nonepisodic, chronic, rapid-cycling, mixed manic state that may be comorbid with ADHD and CD [65]. Several studies have reported that pediatric BAD is characterized by irritable and dysphoric moods, mixed episodes, explosive behavior accompanied by anger attacks, and rapid and ultrarapid cycling with a chronic course [66].

There is a significant loss of functionality in both the disorders. An investigation of the etiology of these two disorders, their effective diagnosis, and treatment are important to keep this loss in functionality to a minimum. One familial study that investigated comorbid ADHD and BAD reported higher rates of ADHD diagnoses in families of subjects with BAD and higher rates of BAD diagnosis in families of subjects diagnosed with ADHD [67]. In addition to genetic factors, potential environmental risk factors for comorbidity have also been investigated [68].

As the presence of comorbidities has an adverse effect on the course of both disorders, early identification and prompt treatment are critical. Different classes of psychopharmacological medications are employed in the treatment of ADHD and BAD, such as stimulants or atomoxetine for ADHD and mood stabilizers or antipsychotics for mania. Problems in differentiating between the two disorders and deciding on the best form of clinical management have important clinical implications for patients. Research also suggests that incorrect treatment may result in nonresponsiveness or worsening of symptoms in the case of ADHD and BAD [69].

## 7. Disruptive mood dysregulation disorder

Researchers regard emotional instability as a core deficit in children diagnosed with ADHD [70]. Therefore, affective instability in children diagnosed with ADHD does not directly indicate the presence of a comorbid mood disorder [71]. The National Institute of Mental Health (NIMH) created a construct for Severe Mood Dysregulation (SMD) to describe such children who do not meet the criteria for a formal mood disorder. Disruptive mood dysregulation disorder (DMDD) took its place in DSM V as a modification of SMD.

ADHD, ODD, and CD are the most common accompanying Axis I diagnoses in children with DMDD [72]. Children with ADHD and SMD experience greater morbidity than children with externalizing behavior disorders alone and are in need of specialized treatment to optimize their functioning [73]. Various behavior modifying therapies and stimulation therapy combinations have been developed for children with comorbid ADHD and SMD, and they have been shown to be effective and acceptable. Research has repeatedly shown that subjects with a diagnosis of SMD exhibited significantly higher levels of functional impairment after a 3-week therapeutic process compared to those with no such diagnosis [74]. It is also important for the parents of children with both these disorders to be referred to parenting programs and family therapy. One study on children with both ADHD and SMD used stimulation therapy at optimal doses prior to their randomization into two groups. One group received treatment involving psychosocial measures for 11 weeks, while the other group took part in group therapy. A significant decrease in suicidal ideation was observed in children receiving group therapy, and their parents also exhibited a more positive parenting behavior [71].

To date, there are too few studies to establish a specific treatment guideline for SMDD. ADHD, the prominent problem in comorbid ADHD and SMDD, can be improved with stimulation therapy. Low-dose antipsychotics can be tried when the basic problems are arousal symptoms and behavioral difficulties.

## 8. Alcohol and substance use disorder

Significantly high rates of development of substance use disorder (SUD), involving use of nicotine, alcohol, marijuana, cocaine, or other drugs, during adolescence have been reported in individuals diagnosed with childhood ADHD [75]. One 10-year study of patients with ADHD showed that the probability of these patients developing substance dependence was twice as high as that of the control group [76]. A study of comorbid psychiatric disorders in subjects with substance abuse disorder reported that half of the adolescents aged under 15 years met the diagnostic criteria for ADHD [77]. Further, early onset and a more severe substance use disorder have been correlated with ADHD. One recent meta-analysis found that childhood ADHD is associated with nicotine use in adolescence and alcohol and drug use disorder in adulthood [78].

As anxiety, depression, and aggression are frequently seen in children and adolescents with ADHD, these patients use substances such as nicotine to self-treat symptoms of anxiety and depression, and nicotine suppresses symptoms of ADHD. Thus, individuals with ADHD use addictive substances to treat psychiatric comorbidities.

One twin study reported that a substance use disorder did not develop in subjects with ADHD without CD [79]. In children diagnosed with ADHD, the group with comorbid CD and/or BAD was at highest risk of developing a substance use disorder [80]. This marked association between ADHD and substance use disorder shows the importance of diagnosing and treating childhood ADHD to avoid the later development of a severe substance use disorder.

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In light of the high comorbidity between ADHD and substance use disorder, it is possible that there are common underlying neurological factors, and ADHD and substance problems also have several common causes.

Variations in dopamine genes that affect attention, arousal, and reinforcement sensitivity are possible common risk factors for the development of ADHD and substance use disorder [81], and altered dopamine (DA) neurotransmission is central to current models of how ADHD and substance abuse disorder develop [82].

As substance abuse itself leads to changes in the brain, it is impossible to determine if individuals with a substance use disorder also exhibit characteristics similar to ADHD or not. However, the changes occurring in the brain due to a substance use disorder are thought to make these individuals more inclined to engage in impulsive behavior, similar to individuals with ADHD but before the onset of the disorder and before the substance abuse. A recent review of neuroimaging studies in humans with ADHD and SUD found repeated evidence of a blunted striatal DA release and a disruption in neural circuitry between the anterior cingulate cortex, the striatum, and the prefrontal cortex. ADHD and SUD-related craving share some neurobiological similarities, which may be because patients with an addiction show increased craving if they also suffer from ADHD [83].

Recent studies have shown that effectively treating ADHD symptoms may be protective in patients with a substance use disorder. The claim that treating ADHD symptoms with stimulants increases the risk for future substance abuse has not been verified, and in fact, the opposite effect is typically seen in medication-treated individuals. Children treated with stimulants appear to have a significantly lower risk of developing a substance use disorder than those who were not pharmacologically treated.

This finding suggests that ADHD does in fact contribute to the development and maintenance of substance use problems, as the successful treatment of ADHD symptoms results in a reduction of the substance use problem [84].

## 9. Developmental coordination disorder

Several studies show a high correlation between ADHD and developmental coordination disorder (DCD). ADHD-DCD comorbidity can be as high as 50% in children [85]. In a study of 477 cases of ADHD, Blondis et al. [86] have reported the presence of a comorbid developmental coordination disorder in at least 33% of the subjects.

Maladroitness in children with ADHD frequently decreases with age, and the children may successfully engage in sporting activities. However, this does not occur in the presence of a comorbid developmental coordination disorder, and it generally persists along with the inattention [86]. Clinical research has shown that maladroitness, clumsiness, and ponderousness seriously affect a child in numerous areas, and that these children find it difficult to perform certain activities at the same speed as their peers in school.

The possible treatment consists of psychological and educational support. Tervo et al. [87] compared the response to methylphenidate in subjects with developmental coordination disorder and ADHD and ADHD alone. They reported that the response to the drug was similar in both the groups and that the stimulant was also effective in treating ADHD.

There are two hypotheses concerning the decrease in symptoms following treatment with methylphenidate. The first is that methylphenidate increases attention, and that increased attention leads to an improvement in motor deficits, while the second is that drug therapy has distinct effects on attention and motor skills.

The proportion of children with ADHD who could improve their motor skills to the normal range upon medication varies from 28% to 67% among reported studies. While the symptoms of patients with a mild motor deficit before treatment improve to normal levels with therapy, in patients with a more severe motor deficit before treatment, the symptoms only decrease in severity and they may still continue to meet the diagnostic criteria for DCD.

It is important to assess motor skills among children with ADHD because of the risk of their reduced participation in daily activities that require motor coordination and attention [88].

## 10. Enuresis and encopresis

ADHD and incontinence are common diseases in childhood, are commonly seen together, and also affect one another. Nocturnal enuresis (NE) is seen in 10% of children aged 7 years, daytime urinary incontinence (DUI) in 2-3% and fecal incontinence (FI), or encopresis in 1-3%. Baeyens et al. [89] have investigated the prevalence of ADHD in 120 children with primary enuresis using parent and teacher questionnaires and diagnostic interviews. Their results indicate that 15% of the children met the criteria for ADHD, and a further 22.5% of them met the criteria for the ADHD inattentive type. A 2-year follow-up study of the same cohort indicated that 73% of those initially diagnosed with ADHD had the diagnosis reconfirmed at follow-up [90]. The authors also noted that the probability of a child with ADHD still having episodes of nocturnal enuresis at 2-year follow-up were 3.2 times higher than that for a child who did not have comorbid ADHD.

There are several hypotheses to explain the comorbidity of ADHD and NE. There is evidence that genetic factors occupy an important place in the etiology of ADHD and NE, as the heritability of NE and ADHD as individual disorders is high. However, the only formal molecular genetics study on both the disorders indicates that NE and ADHD are genetically independent, separate entities that do not share a common genetic basis.

Neuroimaging studies have established a great overlap in brain structures involved in ADHD and NE (and to a lesser extent in DUI and FI); however, a possible interaction between functional brain activity in combined incontinence and ADHD has not yet been studied. It is therefore unclear why and how ADHD and incontinence together affect central nervous system (CNS) functioning. From the few studies on ADHD and NE, it can be speculated that

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complex neural networks, including cortical, subcortical, and brainstem regions, will most likely be responsible for the clinically evident interaction effects [91].

Incontinence must be investigated in children with ADHD, and ADHD must be investigated in children with incontinence. The management of enuresis includes supportive approaches such as educating parents about enuresis, reducing fluids, keeping a dry bed chart, and awakening the child to void during the night, conditioning with a urine alarm, or medications such as imipramine or desmopressin acetate [92]. Treatment must be adapted to include both supportive approaches and pharmacotherapy in patients with ADHD and incontinence.

One double-blind, placebo-controlled study investigating the effectiveness of atomoxetine in children with NE reported a significant decrease in symptoms. Atomoxetine, a highly specific inhibitor of the presynaptic norepinephrine transporter, increases the effects of norepinephrine in many brain areas. Atomoxetine-mediated decrease in symptoms of NE supports the hypothesis that these drugs, with their noradrenergic effect, may be beneficial in the treatment of this disease [93]. NE and ADHD may improve with both methylphenidate and atomoxetine. Many hypotheses have been proposed—involving central neurochemical dysfunctions (dopaminergic and noradrenergic), anticholinergic, and reduced sleep arousal effects of these drugs—to account for the effects of these medications in the treatment of enuresis and ADHD [94, 95].

Studies aimed at understanding the relationship between ADHD and elimination disorders may identify common, underlying neurological alterations that may lead to a more effective treatment for both the disorders [96].

## 11. Tic disorders

Tic disorders are quite rare in the general population but are common in the population with ADHD. Tic comorbidity in patients with ADHD ranges between 8% and 10% [97, 98], and ADHD is the most common accompanying disorder in tic patients [99].

Tic disorders have little effect on the psychosocial functioning of subjects with ADHD [100]. There is no definitive evidence regarding the course of ADHD being affected by the tic disorder. However, accompanying obsessive-compulsive symptoms have been reported in a significant proportion of individuals with ADHD and comorbid tic disorders. Tics, OCD, and ADHD are related in a number of complex ways and have common demographic and psychopathological risk factors [101].

Greater psychopathology and social and academic impairment have been reported when ADHD is comorbid with Tourette's disease [102]. Earlier age at onset, greater difficulty of anger control, sleep problems, ODD, mood disorders, deficient social skills, inappropriate sexual behavior, and self-harming behaviors are seen when Tourette's syndrome is comorbid with ADHD [103].

The pathophysiology of ADHD and the tic disorder is unclear, although their comorbidity suggests that they have similar mechanisms or at least that they are compatible to varying

degrees [104]. These two disorders share a number of genetic, neuronal, and cognitive risk factors, and several dopamine and serotonin genes have been studied as potential risk factors. Genes and environmental risk factors are also thought to cause both disorders. Abnormalities in the same anatomical cycle, such as cortical thinning, frontal system abnormalities, and basal ganglia abnormalities, have been shown in children with Tourette's and ADHD [105].

A comprehensive treatment program for Tourette's syndrome and comorbid ADHD should include measures other than medication such as cognitive-behavioral, psychoeducational, and psychosocial interventions.

Three classes of drugs are currently used in the treatment of Tourette's syndrome and comorbid ADHD: $\alpha$-agonists (clonidine and guanfacine), stimulants (amphetamine enantiomers, methylphenidate enantiomers or slow release preparations), and selective norepinephrine reuptake inhibitors (atomoxetine). It has been recently suggested that in a few selected cases partial dopamine agonists (aripiprazole) could be useful, and there is evidence supporting the use of noradrenergic agents (clonidine). Reuptake inhibitors (atomoxetine) and stimulants (methylphenidate) could also be used for the treatment of Tourette's syndrome and comorbid ADHD [106]. Although the evidence is insufficient, there are studies that suggest using aripiprazole in children with mild ADHD [107].

## 12. Conclusion

ADHD is associated with several comorbid psychiatric diseases and conditions, and these comorbid conditions may cause a worsening of the symptoms of ADHD. Greater loss of functionality is observed in patients with a comorbid condition. It is important to diagnose and treat these comorbid conditions to effectively treat ADHD.

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## References

[1] Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. Biological Psychiatry. 2005;57(11):1215-20.

[2] Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. Journal of Pediatric Psychology. 2007;32(6):631-42.

[3] Biederman J, Petty CR, O'Connor KB, Hyder LL, Faraone SV. Predictors of persistence in girls with attention deficit hyperactivity disorder: results from an 11-year controlled follow-up study. Acta Psychiatrica Scandinavica. 2012;125(2):147-56.

[4] Jensen PS, Martin D, Cantwell DP. Comorbidity in ADHD: implications for research, practice, and DSM-V Journal of the American Academy of Child and Adolescent Psychiatry. 1997;36(8):1065-79.

[5] Gau SS-F, Ni H-C, Shang C-Y, Soong W-T, Wu Y-Y, Lin L-Y, et al. Psychiatric comorbidity among children and adolescents with and without persistent attention-deficit hyperactivity disorder. Australian and New Zealand Journal of Psychiatry. 2010;44(2):135-43.

[6] Huh Y, Choi I, Song M, Kim S, Hong SD, Joung Y. A comparison of comorbidity and psychological outcomes in children and adolescents with attention-deficit/hyperactivity disorder. Psychiatry Investigation. 2011;8(2):95-101.

[7] Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. American Journal of Psychiatry. 1991.

[8] Pliszka SR. Psychiatric comorbidities in children with attention deficit hyperactivity disorder. Pediatric Drugs. 2003;5(11):741-50.

[9] Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, et al. Patterns and predictors of ADHD persistence into adulthood: results from the National Comorbidity Survey Replication. Biological Psychiatry. 2005;57(11):1442.

[10] Semerci Z. Attention deficit hyperactivity disorder comorbidity in children and adolescents with Gilles de La Tourette syndrome. Çocuk ve Gençlik Ruh Sağlığı Dergisi/ Turkish Journal of Child and Adolescent Mental Health. 2001;8(1):19-26.

[11] Wiśniewska B, Baranowska W, Wendorff J. The assessment of comorbid disorders in ADHD children and adolescents. Advances in Medical Sciences. 2006;52:215-7.

[12] Ghanizadeh A. Psychiatric comorbidity differences in clinic-referred children and adolescents with ADHD according to the subtypes and gender. Journal of Child Neurology. 2009;24(6):679-84.

[13] Yuce M, Zoroglu SS, Ceylan MF, Kandemir H, Karabekiroglu K. Psychiatric comorbidity distribution and diversities in children and adolescents with attention deficit/ hyperactivity disorder: a study from Turkey. Neuropsychiatric Disease and Treatment. 2013;9:1791-9.

[14] Waxmonsky J. Assessment and treatment of attention deficit hyperactivity disorder in children with comorbid psychiatric illness. Current Opinion in Pediatrics. 2003;15(5):476-82.

[15] Biederman J, Faraone SV, Taylor A, Sienna M, Williamson S, Fine C. Diagnostic continuity between child and adolescent ADHD: findings from a longitudinal clinical sample. Journal of the American Academy of Child and Adolescent Psychiatry. 1998;37(3):305-13.

[16] Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Spencer T, et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. American Journal of Psychiatry. 2002;159(1):36-42.

[17] Chen M-H, Su T-P, Chen Y-S, Hsu J-W, Huang K-L, Chang W-H, et al. Higher risk of developing mood disorders among adolescents with comorbidity of attention deficit hyperactivity disorder and disruptive behavior disorder: a nationwide prospective study. Journal of Psychiatric Research. 2013;47(8):1019-23.

[18] Greene RW, Biederman J, Zerwas S, Monuteaux MC, Goring JC, Faraone SV. Psychiatric comorbidity, family dysfunction, and social impairment in referred youth with oppositional defiant disorder. American Journal of Psychiatry. 2002;159(7):1214-24.

[19] Nordström T, Hurtig T, Moilanen I, Taanila A, Ebeling H. Disruptive behaviour disorder with and without attention deficit hyperactivity disorder is a risk of psychiatric hospitalization. Acta Paediatrica. 2013;102(11):1100-3.

[20] Thapar A, Harrington R, McGUFFIN P. Examining the comorbidity of ADHD-related behaviours and conduct problems using a twin study design. British Journal of Psychiatry. 2001;179(3):224-9.

[21] Saarinen S, Fontell T, Vuontela V, Carlson S, Aronen ET. Visuospatial working memory in 7-to 12-year-old children with disruptive behavior disorders. Child Psychiatry and Human Development. 2014:1-10.

[22] Biederman J, Faraone SV, Milberger S, Jetton JG, Chen L, Mick E, et al. Is childhood oppositional defiant disorder a precursor to adolescent conduct disorder? Findings from a four-year follow-up study of children with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry. 1996;35(9):1193-204.

[23] Biederman J, Petty C, Dolan C, Hughes S, Mick E, Monuteaux M, et al. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. Psychological Medicine. 2008;38(07):1027-36.

[24] Barkley RA, Fischer M, Edelbrock C, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria—III. Mother-child interactions, family conflicts and maternal psychopathology. Journal of Child Psychology and Psychiatry. 1991;32(2):233-55.

[25] Steiner H. Practice parameters for the assessment and treatment of children and adolescents with conduct disorder. American Academy of Child and Adolescent Psychiatry. Journal of the American Academy of Child and Adolescent Psychiatry. 1997;36(10 Suppl):122S-39S.

[26] Wilson JM, Marcotte AC. Psychosocial adjustment and educational outcome in adolescents with a childhood diagnosis of attention deficit disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 1996;35(5):579-87.

[27] Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Library. 2012.

[28] Gadow KD, Arnold LE, Molina BS, Findling RL, Bukstein OG, Brown NV, et al. Risperidone added to parent training and stimulant medication: effects on attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, and peer aggression. Journal of the American Academy of Child and Adolescent Psychiatry. 2014;53(9):948-59. e1.

[29] Ercan ES, Uysal T, Ercan E, Ardıc U. Aripiprazole in children and adolescents with conduct disorder: a single-center, open-label study. Pharmacopsychiatry. 2012;45(1): 13-9.

[30] NM M. Yaşam Boyu Dikkat Eksikliği Hiperaktivite Bozukluğu ve Eşlik Eden Durumlar. Nobel Tıp Kitabevi. 2015.

[31] Mayes SD, Calhoun SL. Similarities and differences in Wechsler Intelligence Scale for Children—Third Edition (WISC-III) profiles: support for subtest analysis in clinical referrals. Clinical Neuropsychologist. 2004;18(4):559-72.

[32] Mayes SD, Calhoun SL. Frequency of reading, math, and writing disabilities in children with clinical disorders. Learning and Individual Differences. 2006;16(2):145-57.

[33] Mayes SD, Calhoun SL. Wechsler Intelligence Scale for Children—Third and Fourth Edition: predictors of academic achievement in children with attention-deficit/hyperactivity disorder. School Psychology Quarterly. 2007;22(2):234.

[34] Morgan AE, Hynd GW, Riccio CA, Hall J. Validity of DSM-IV ADHD predominantly inattentive and combined types: relationship to previous DSM diagnoses/subtype differences. Journal of the American Academy of Child and Adolescent Psychiatry. 1996;35(3):325-33.

[35] DuPaul GJ, Gormley MJ, Laracy SD. Comorbidity of LD and ADHD: implications of DSM-5 for assessment and treatment. Journal of learning disabilities. 2012:0022219412464351.

[36] Sexton CC, Gelhorn H, Bell J, Classi P. The co-occurrence of reading disorder and ADHD: epidemiology, treatment, psychosocial impact, and economic burden. Journal of Learning Disabilities. 2011:0022219411407772.

[37] ABALI O. Attention deficit hyperactivity disorder and learning disorder. Turkiye Klinikleri Journal of Pediatrical Sciences. 2010;6(2):22.

[38] Williamson D, Murray DW, Damaraju C, Ascher S, Starr HL. Methylphenidate in children with ADHD with or without learning disability. Journal of Attention Disorders. 2014;18(2):95-104.

[39] Shaywitz BA, Williams DW, Fox BK, Wietecha LA. Reading outcomes of children and adolescents with attention-deficit/hyperactivity disorder and dyslexia following atomoxetine treatment. Journal of Child and Adolescent Psychopharmacology. 2014;24(8):419-25.

[40] Bolea-Alamañac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology. 2014;28(3):179-203.

[41] Baker BL, Neece CL, Fenning RM, Crnic KA, Blacher J. Mental disorders in five-year-old children with or without developmental delay: focus on ADHD. Journal of Clinical Child and Adolescent Psychology. 2010;39(4):492-505.

[42] Neece C, Baker B, Blacher J, Crnic K. Attention-deficit/hyperactivity disorder among children with and without intellectual disability: an examination across time. Journal of Intellectual Disability Research. 2011;55(7):623-35.

[43] Pearson DA, Santos CW, Roache JD, Casat CD, Loveland KA, Lachar D, et al. Treatment effects of methylphenidate on behavioral adjustment in children with mental retardation and ADHD. Journal of the American Academy of Child and Adolescent Psychiatry. 2003;42(2):209-16.

[44] Simonoff E, Taylor E, Baird G, Bernard S, Chadwick O, Liang H, et al. Randomized controlled double-blind trial of optimal dose methylphenidate in children and adolescents with severe attention deficit hyperactivity disorder and intellectual disability. Journal of Child Psychology and Psychiatry. 2013;54(5):527-35.

[45] Weber P, Lütschg J. Methylphenidate treatment. Pediatric Neurology. 2002;26(4): 261-6.

[46] Aman MG, Smith T, Arnold LE, Corbett-Dick P, Tumuluru R, Hollway JA, et al. A review of atomoxetine effects in young people with developmental disabilities. Research in Developmental Disabilities. 2014;35(6):1412-24.

[47] Fernández-Jaén A, Fernández-Mayoralas DM, Calleja Pérez B, Muñoz Jareño N, del Rosario Campos Díaz M. Atomoxetine for attention deficit hyperactivity disorder in mental retardation. Pediatric Neurology. 2010;43(5):341-7.

[48] Eugene Arnold L. Commentary: filling out the evidence base for treatment of attention-deficit hyperactivity disorder symptoms in children with intellectual and devel-

opmental disability: conclusions for clinicians—a response to Simonoff et al. (2013). Journal of Child Psychology and Psychiatry. 2013;54(6):701-3.

[49] Biederman J, Faraone S, Milberger S, Guite J, Mick E, Chen L, et al. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. Archives of General Psychiatry. 1996;53(5):437-46.

[50] Biederman J, Faraone S, Mick E, Lelon E. Psychiatric comorbidity among referred juveniles with major depression: fact or artifact? Journal of the American Academy of Child and Adolescent Psychiatry. 1995;34(5):579-90.

[51] Meinzer MC, Pettit JW, Viswesvaran C. The co-occurrence of attention-deficit/hyperactivity disorder and unipolar depression in children and adolescents: a meta-analytic review. Clinical Psychology Review. 2014.

[52] Connor DF, Edwards G, Fletcher KE, Baird J, Barkley RA, Steingard RJ. Correlates of comorbid psychopathology in children with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry. 2003;42(2):193-200.

[53] Cohen R, Lohr I, Paul R, Boland R. Impairments of attention and effort among patients with major affective disorders. Journal of Neuropsychiatry and Clinical Neurosciences. 2001;13(3):385-95.

[54] Biederman J, Ball SW, Monuteaux MC, Mick E, Spencer TJ, McCreary M, et al. New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. Journal of the American Academy of Child and Adolescent Psychiatry. 2008;47(4):426-34.

[55] Di Trani M, Di Roma F, Elda A, Daniela L, Pasquale P, Silvia M, et al. Comorbid depressive disorders in ADHD: the role of ADHD severity, subtypes and familial psychiatric disorders. Psychiatry Investigation. 2014;11(2):137-42.

[56] Chen MH, Chen YS, Hsu JW, Huang KL, Li CT, Lin WC, et al. Comorbidity of ADHD and subsequent bipolar disorder among adolescents and young adults with major depression: a nationwide longitudinal study. Bipolar Disorders. 2014.

[57] Roy A, Oldehinkel AJ, Verhulst FC, Ormel J, Hartman CA. Anxiety and disruptive behavior mediate pathways from attention-deficit/hyperactivity disorder to depression. Journal of Clinical Psychiatry. 2014;75(2):e108-13.

[58] Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Newcorn JH, Abikoff HB, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. Journal of the American Academy of Child and Adolescent Psychiatry. 2001;40(2):147-58.

[59] Schatz DB, Rostain AL. ADHD with comorbid anxiety a review of the current literature. Journal of Attention Disorders. 2006;10(2):141-9.

[60] Faraone SV, Biederman J. Do attention deficit hyperactivity disorder and major depression share familial risk factors? Journal of Nervous and Mental Disease. 1997;185(9):533-41.

[61] Kratochvil CJ, May DE, Silva SG, Madaan V, Puumala SE, Curry JF, et al. Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. Journal of Child and Adolescent Psychopharmacology. 2009;19(5):519-27.

[62] Daviss WB. A review of co-morbid depression in pediatric ADHD: etiologies, phenomenology, and treatment. Journal of Child and Adolescent Psychopharmacology. 2008;18(6):565-71.

[63] Biederman J, Faraone S, Mick E, Wozniak J, Chen L, Ouellette C, et al. Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? Journal of the American Academy of Child and Adolescent Psychiatry. 1996;35(8):997-1008.

[64] Arnold LE, Demeter C, Mount K, Frazier TW, Youngstrom EA, Fristad M, et al. Pediatric bipolar spectrum disorder and ADHD: comparison and comorbidity in the LAMS clinical sample. Bipolar Disorders. 2011;13(5-6):509-21.

[65] Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. Journal of the American Academy of Child and Adolescent Psychiatry. 1997;36(9):1168-76.

[66] LUŞ MG. Bipolar Bozukluk ve Dikkat Eksikliği Hiperaktivite Bozukluğu. Türkiye Klinikleri Pediatrik Bilimler Dergisi. 2010;6(2):31-7.

[67] Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? Journal of the American Academy of Child and Adolescent Psychiatry. 1997;36(10):1378-90.

[68] Surman CB, Biederman J, Spencer T, Yorks D, Miller CA, Petty CR, et al. Deficient emotional self-regulation and adult attention deficit hyperactivity disorder: a family risk analysis. American Journal of Psychiatry. 2011;168(6):617-23.

[69] Skirrow C, Hosang GM, Farmer AE, Asherson P. An update on the debated association between ADHD and bipolar disorder across the lifespan. Journal of Affective Disorders. 2012;141(2):143-59.

[70] Martel MM. Research review: a new perspective on attention-deficit/hyperactivity disorder: emotion dysregulation and trait models. Journal of Child Psychology and Psychiatry. 2009;50(9):1042-51.

[71] Waxmonsky JG, Wymbs FA, Pariseau ME, Belin PJ, Waschbusch DA, Babocsai L, et al. A novel group therapy for children with ADHD and severe mood dysregulation. Journal of Attention Disorders. 2012:1087054711433423.

[72] Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biological Psychiatry. 2006;60(9):991-7.

[73] Anastopoulos AD, Smith TF, Garrett ME, Morrissey-Kane E, Schatz NK, Sommer JL, et al. Self-regulation of emotion, functional impairment, and comorbidity among children with AD/HD. Journal of Attention Disorders. 2011;15(7):583-92.

[74] Waxmonsky J, Pelham WE, Gnagy E, Cummings MR, O'Connor B, Majumdar A, et al. The efficacy and tolerability of methylphenidate and behavior modification in children with attention-deficit/hyperactivity disorder and severe mood dysregulation. Journal of Child and Adolescent Psychopharmacology. 2008;18(6):573-88.

[75] Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clinical Psychology Review. 2011;31(3):328-41.

[76] Biederman J, Monuteaux MC, Mick E, Spencer T, Wilens TE, Silva JM, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychological Medicine. 2006;36(02):167-79.

[77] Chan Y-F, Dennis ML, Funk RR. Prevalence and comorbidity of major internalizing and externalizing problems among adolescents and adults presenting to substance abuse treatment. Journal of Substance Abuse Treatment. 2008;34(1):14-24.

[78] Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. Journal of the American Academy of Child and Adolescent Psychiatry. 2011;50(1):9-21.

[79] Disney ER, Elkins IJ, McGue M, Iacono WG. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. American Journal of Psychiatry. 1999;156(10):1515-21.

[80] Wilens TE, Morrison NR. The intersection of attention-deficit/hyperactivity disorder and substance abuse. Current Opinion in Psychiatry. 2011;24(4):280.

[81] Milberger S, Faraone SV, Biederman J, Chu MP, Wilens T. Familial risk analysis of the association between attention-deficit/hyperactivity disorder and psychoactive substance use disorders. Archives of Pediatrics and Adolescent Medicine. 1998;152(10):945-51.

[82] Volkow N, Fowler J, Wang G, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. 2009;56:3-8.

[83] Frodl T. Comorbidity of ADHD and substance use disorder (SUD): a neuroimaging perspective. Journal of Attention Disorders. 2010;14(2):109-20.

[84] Looby A. Childhood attention deficit hyperactivity disorder and the development of substance use disorders: valid concern or exaggeration? Addictive Behaviors. 2008;33(3):451-63.

[85] Kadesjo B, Gillberg C. Developmental coordination disorder in Swedish 7-year-old children. Journal of the American Academy of Child and Adolescent Psychiatry. 1999;38(7):820-8.

[86] Blondis TA. Motor disorders and attention-deficit/hyperactivity disorder. Pediatric Clinics of North America. 1999;46(5):899-913.

[87] Tervo RC, Azuma S, Fogas B, Fiechtner H. Children with ADHD and motor dysfunction compared with children with ADHD only. Developmental Medicine and Child Neurology. 2002;44(6):383-90.

[88] Kaiser M-L, Schoemaker M, Albaret J-M, Geuze R. What is the evidence of impaired motor skills and motor control among children with attention deficit hyperactivity disorder (ADHD)? Systematic review of the literature. Research in Developmental Disabilities. 2015;36:338-57.

[89] Baeyens D, Roeyers H, Hoebeke P, Verte S, Van Hoecke E, Walle JV. Attention deficit/hyperactivity disorder in children with nocturnal enuresis. Journal of Urology. 2004;171(6):2576-9.

[90] Baeyens D, Roeyers H, Demeyere I, Verte S, Hoebeke P, Walle JV. Attention-deficit/hyperactivity disorder (ADHD) as a risk factor for persistent nocturnal enuresis in children: a two-year follow-up study. Acta Paediatrica. 2005;94(11):1619-25.

[91] von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. European Child and Adolescent Psychiatry. 2014:1-14.

[92] Action AO. Practice parameters for the assessment and treatment of children and adolescents with enuresis. Journal of the American Academy of Child and Adolescent Psychiatry. 2004;43:1540-50.

[93] Sumner CR, Schuh KJ, Sutton VK, Lipetz R, Kelsey DK. Placebo-controlled study of the effects of atomoxetine on bladder control in children with nocturnal enuresis. Journal of Child and Adolescent Psychopharmacology. 2006;16(6):699-711.

[94] Williamson LB, Gower M, Ulzen T. Clinical case rounds in child and adolescent psychiatry: enuresis and ADHD in older children and an adolescent treated with stimulant medication: a case series. Journal of the Canadian Academy of Child and Adolescent Psychiatry. 2011;20(1):53.

[95] Crimmins C, Rathbun S, Husmann D. Management of urinary incontinence and nocturnal enuresis in attention-deficit hyperactivity disorder. Journal of Urology. 2003;170(4):1347-50.

[96] Mellon MW, Natchev BE, Katusic SK, Colligan RC, Weaver AL, Voigt RG, et al. Incidence of enuresis and encopresis among children with attention-deficit/hyperactivity disorder in a population-based birth cohort. Academic Pediatrics. 2013;13(4):322-7.

[97] Steinhausen H-C, Nøvik TS, Baldursson G, Curatolo P, Lorenzo MJ, Pereira RR, et al. Co-existing psychiatric problems in ADHD in the ADORE cohort. European Child and Adolescent Psychiatry. 2006;15(1):i25-i9.

[98] Swanson J, Lerner M, March J, Gresham FM. Assessment and intervention for attention-deficit/hyperactivity disorder in the schools: lessons from the MTA study. Pediatric Clinics of North America. 1999;46(5):993-1009.

[99] Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. Developmental Medicine and Child Neurology. 2000;42(7):436-47.

[100] Spencer T, Biederman J, Coffey B, Geller D, Wilens T, Faraone S. The 4-year course of tic disorders in boys with attention-deficit/hyperactivity disorder. Archives of General Psychiatry. 1999;56(9):842-7.

[101] Peterson BS, Pine DS, Cohen P, Brook JS. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. Journal of the American Academy of Child and Adolescent Psychiatry. 2001;40(6):685-95.

[102] Gorman DA, Thompson N, Plessen KJ, Robertson MM, Leckman JF, Peterson BS. Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette syndrome: controlled study. British Journal of Psychiatry. 2010;197(1):36-44.

[103] Freeman RD. Tic disorders and ADHD: answers from a world-wide clinical dataset on Tourette syndrome. European Child and Adolescent Psychiatry. 2007;16(9):15-23.

[104] Steeves TD, Fox SH. Neurobiological basis of serotonin-dopamine antagonists in the treatment of Gilles de la Tourette syndrome. Progress in brain research. 2008;172:495-513.

[105] Murphy T, Muter V. Risk factors for comorbidity in ADHD and GTS: looking beyond a single-deficit model. Applied Neuropsychology: Child. 2012;1(2):129-36.

[106] Rizzo R, Gulisano M, Calì PV, Curatolo P. Tourette Syndrome and comorbid ADHD: current pharmacological treatment options. European Journal of Paediatric Neurology. 2013;17(5):421-8.

[107] Masi G, Gagliano A, Siracusano R, Berloffa S, Calarese T, Ilardo G, et al. Aripiprazole in children with Tourette's disorder and co-morbid attention-deficit/hyperactivity disorder: a 12-week, open-label, preliminary study. Journal of Child and Adolescent Psychopharmacology. 2012;22(2):120-5.

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