



# ADHD and Anxiety Disorder Comorbidity in Children and Adults: Diagnostic and Therapeutic Challenges

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## Abstract

**Purpose of the Review** In this review, we focus on overlapping features of ADHD and anxiety disorders, and will discuss how an anxiety disorder comorbidity leads to diagnostic and treatment challenges in patients with ADHD, in consideration of the accumulated available knowledge.

**Recent Findings** The presence of overlapping symptoms, changes in the diagnostic criteria, and the use of divergent diagnostic tools and informant effects can complicate the diagnosis of this comorbidity. Due to the ongoing debate about the etiology, psychopathology, and diagnostic features of the association between ADHD and anxiety disorders, choosing appropriate treatment options emerges as a challenge.

**Summary** A novel methodology, standardized interview tools, and new statistical analysis methods are needed to define the phenotype of this co-occurrence more clearly. It is important to uncover the developmental nature of this comorbidity with follow-up studies that may explain the etiology and underlying neurobiological basis, and ultimately lead to more effective treatment approaches.

**Keywords** ADHD · Anxiety disorder · Social anxiety disorder · Comorbidity · Diagnosis · Treatment

## Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common disorder that is constituted of three major components: inattention, hyperactivity, and impulsivity, and it creates difficulties in children's school, family, and social life [1]. The prevalence of ADHD is about 5–7% in children and adolescents [2–5] and about 3–4.5% in adult patients [6, 7]. ADHD is an early-onset disorder;

however, recent studies have reported that ADHD is not solely a childhood disorder, but also it persists into adulthood [8–11].

Anxiety disorders are one of the most common comorbidities with a prevalence of approximately 25–50% in patients with ADHD [12••]. There are epidemiological and clinical studies that indicated high rates of anxiety disorder comorbidity in both child and adolescent [13–16] and adult [6, 17, 18] patients with ADHD. One of these epidemiological studies showed that approximately 47% of adults who have ADHD diagnosis also have a comorbid anxiety disorder [6]. Another study

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that included 473 college students found that participants with ADHD have higher levels of anxiety than the control group [19]. Patients with ADHD plus comorbid anxiety disorders have more severe ADHD symptoms [12••, 20], more psychiatric comorbidities, and an earlier age of onset than ADHD patients without anxiety disorders [12••, 21]. Although high rates of comorbidity have been reported between ADHD and anxiety disorders, discussions on the etiology, diagnosis, and treatment options of this association still continue.

There is growing evidence suggesting that ADHD and anxiety have a complex relationship, such as one disorder leads to the occurrence of another or affects another's course. In the present review, we focus on overlapping features of ADHD and anxiety disorder co-occurrence, and we will discuss how anxiety disorder comorbidity leads to diagnostic and treatment challenges in patients with ADHD, in consideration of the accumulated available knowledge. The literature investigation was conducted in PubMed and Google Scholar with the following terms: "Attention deficit/ hyperactivity disorder," "ADHD," "comorbidity," "anxiety," "anxiety disorders," "panic disorder," "generalized anxiety disorders," "social anxiety disorder," "specific phobia," "diagnostic difficulties," "treatment." While doing literature search, references of primary articles (original articles, brief reports, review articles, case reports/series) are also included. Only academically valued reports and articles in English were involved in this review article.

## The Complex Association Between ADHD and Anxiety Disorders

There are several hypotheses proposed about the co-occurrence of ADHD and anxiety disorders. The first hypothesis about this relationship is that both disorders are pathophysiologically distinct entities that overlap by chance [22, 23]. However, it is also suggested that the frequency of this comorbidity is found to be too high to be explained by chance or referral bias alone [23, 24, 25••].

The second hypothesis suggests that both disorders share the same underlying mechanism which is explained by shared heritability [23, 26]. Michelini et al. (2015) proposed that this co-occurrence may be partially explained by genetic and environmental factors [27]. Moreover, the relatives of ADHD probands might have increased risk for diagnosing with anxiety disorders, yet both disorders cannot co-segregate within families [28, 29]. Segenreich et al. (2015) reported that while maternal variables significantly correlated, the paternal variables do not correlate with offspring variables [30]. These results supported that the genetic component of ADHD and anxiety may share some commonalities; therefore, they may co-exist, but transmission of the genetic elements occurs independently [23]. Further comprehensive research is needed to show the contributions of genetic and environmental factors in the emergence of this comorbidity.

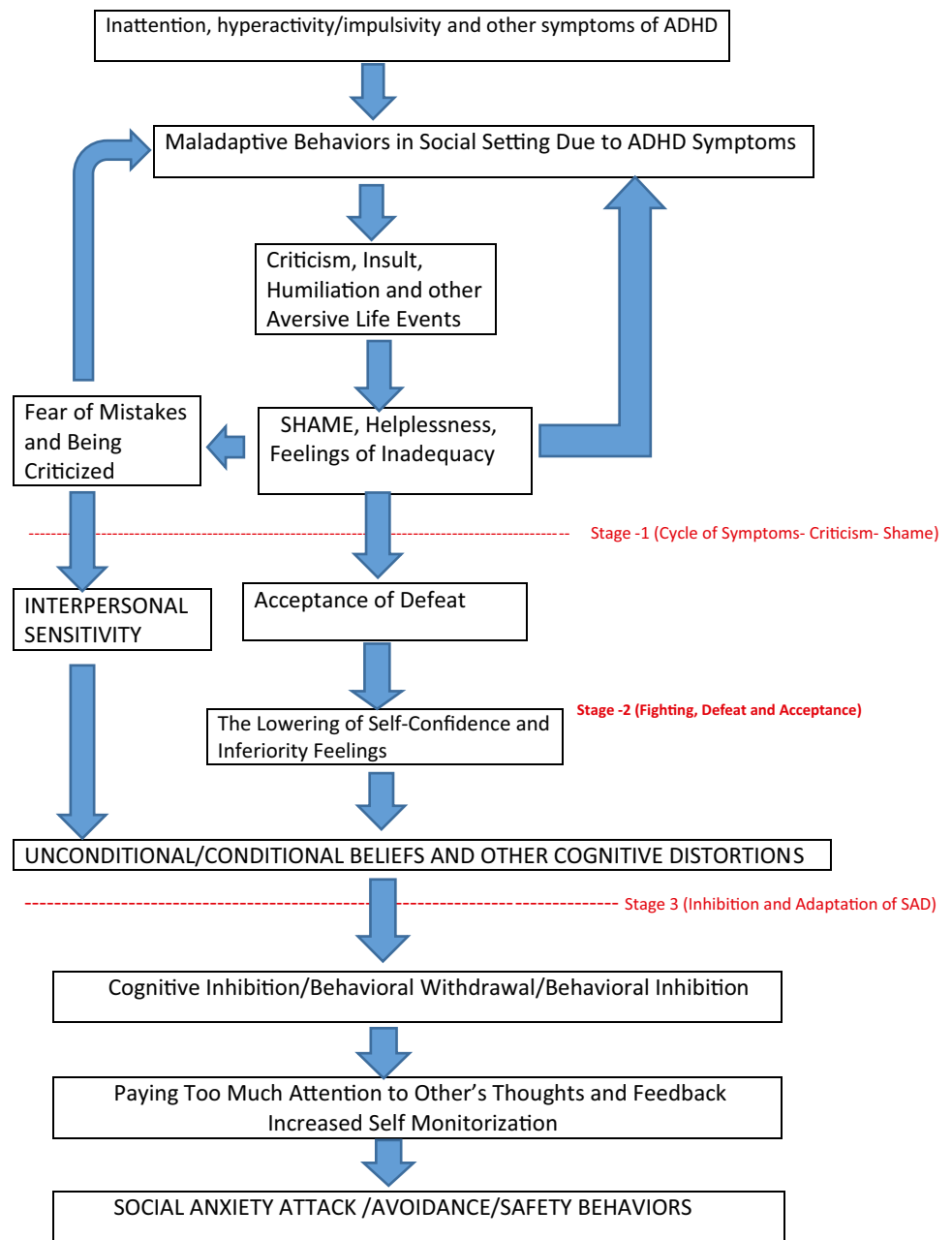
The third hypothesis is that one disorder leads to secondary development of another disorder. In a comprehensive explanation of ADHD and anxiety disorders, Tannock (2000) put forward various arguments to understand this comorbidity, and came to the conclusion that there may be more than one hypothesis to explain the development of these co-occurrences [31]. For example, according to one opinion, anxiety may occur as a result of persistent negative experiences caused by ADHD symptoms, and according to another, inattention may develop secondary to anxiety [14, 31]. In addition to these hypotheses, Nigg et al. (2004) proposed two pathways for the development of these comorbid conditions. First, early deficits in the regulatory system might result in impairments in the regulation of anxiety. The second, cognitive or regulatory dysfunction might occur secondary to increased anxiety [14, 32].

Although recent studies have supported the notion that patients with ADHD are at greater risk for later development of an anxiety disorder [12••], there is no definite evidence on whether anxiety disorders develop secondary to ADHD [33•]. However, there are increasing number of studies supporting a causal relationship between ADHD and anxiety disorders [12••, 23, 24, 35•]. There are longitudinal studies showing that the rates of lifetime anxiety disorder development were higher in children and adolescents with ADHD than in control groups [34, 36–40]. In an 11-year follow-up study, it was reported that patients with ADHD developed a higher level of anxiety disorders than the control group (17.7% vs 1.9%, respectively) [34]. They suggested that early diagnosis and treatment for patients with ADHD may prevent later development of anxiety disorders. In a community-based longitudinal study, Murray et al. (2020) found that there was a reciprocal developmental relationship between ADHD and anxiety in adolescent participants [33•]. They posited that adolescents who have anxiety symptoms should be carefully evaluated for underlying ADHD diagnosis and adolescents with ADHD symptoms are also monitored for the emergence of anxiety symptoms; thus, they have an opportunity accessing preventive interventions, early diagnosis, and treatment [33•].

Regarding this causal relationship, various ideas have emerged. For example, Jensen et al. (1997) suggested that ADHD and comorbid anxiety might be considered a separate ADHD subtype [41]. On the other hand, in two other studies conducted in patients with social anxiety disorder (SAD), it was found that predominantly inattentive type of ADHD was associated with SAD [42, 43•]. These results were replicated in a study conducted in a child and adolescent population with ADHD [44].

In a developmental hypothesis proposed by Koyuncu et al. (2018), we posited that the development of SAD secondary to ADHD may be a distinct subgroup among patients with SAD [45••] (Fig. 1). On the other hand, Pliszka (2019)

**Fig. 1** The hypothesis of SAD development secondary to childhood ADHD (based on Koyuncu et al. (2018) Fig. 1) (ADHD attention deficit/hyperactivity disorder, SAD social anxiety disorder)



suggested that when psychostimulants alleviate anxiety, this might stem from the idea that the anxiety is considered secondary to the stress of the impairment caused by ADHD and that “secondary anxiety” cannot be the complete story [25••, 46]. In line with Plizska (2019), in the developmental hypothesis, we assumed that ADHD is not the sole cause of SAD development; however, ADHD might be one of the vulnerability factor for developing anxiety [25••]. SAD may occur in the context of ADHD when it is combined with other factors including parental attitudes, difficulties in social life, and aversive life conditions resulted from ADHD (Fig. 1) [45••]. Deriving from these ideas, we proposed a 3-stage prodromal period, named as pre-social anxiety,

that corresponds to the process in which SAD develops in the context of ADHD as seen in psychosis (pre-psychosis) or cancer (pre-cancer) patients (Fig. 1). According to the authors, if the hypothesis is proven, SAD could be captured in the prodrome period and treated before the full-blown illness emerges [45••].

Treatment studies have been proposed as evidence supporting that there is a causal relationship between ADHD and anxiety. While earlier studies support that anxiety can diminish the response to stimulants in patients with ADHD with comorbid anxiety disorders [47–49], on the contrary, later studies have reported that ADHD treatments are effective to reduce comorbid anxiety symptoms in patients with

ADHD with comorbid anxiety disorders [50–57]. In a 10-year follow-up study, Biederman et al. (2009) reported that individuals with ADHD who took psychostimulant treatment had lower rates of development of subsequent depressive symptoms, anxiety disorders, and disruptive behaviors than individuals with ADHD who did not take [58].

## What Is the Role of Anxiety on ADHD Components?

In addition to discussions on the causality between the two disorders, there are also studies investigating the mutual interaction between ADHD components such as inattention or hyperactivity/impulsivity and anxiety. According to Pliszka (2019), there has been a continued debate as to whether anxiety symptoms in the patients with ADHD lead to exacerbation or attenuation of attention or impulsivity components [25••]. Regarding this topic, Pallanti and Salerno (2020) assumed that the co-occurrence of ADHD and anxiety was characterized by a bidirectional association, implies that both disorders might affect each other [12••]. Micheline et al. (2015) reported that there are moderate associations between inattention and the anxiety disorders subtypes, whereas the relations between hyperactivity/impulsivity and anxiety disorders subtypes were negligible [27]. Moreover, attention deficit problems can be anxiogenic [23, 59] and the presence of anxiety may make inattention worse [60, 61]. According to Weiss et al. (2011), the cognitive impairments caused by ADHD may produce anxiety and this anxiety may exacerbate the symptoms of inattention. This condition creates a vicious circle [23]. Working memory may be an important structure of the impairment in ADHD with comorbid anxiety disorders conditions [21, 23, 46, 47]. Attention problems and anxiety disorders are impelled by working memory difficulties and both also induce problems with working memory. Thus, these three symptoms are intertwined [23]. On the other hand, there are also studies investigating the relationship between the impulsivity component of ADHD and anxiety. Pliszka (1992) suggests that children with ADHD plus anxiety might be less impulsive and/or hyperactive than children who have ADHD alone [62]. In a review, Scratz and Rostain (2006) reported that anxiety in patients with ADHD can partially inhibit impulsiveness and response inhibition deficits [21]. Moreover, in a large population-derived adolescent study, it was found that social anxiety scores have a negative correlation with hyperactivity/impulsivity scores [27]. Contrary to studies that highlight the relationship between the inattention component of ADHD and anxiety, Prevatt et al. (2016) indicated that anxiety and inattention have a relationship similar to the relationship between hyperactivity/impulsivity and anxiety in

ADHD group [19]. These results also support the hypothesis that anxiety reduces impulsivity proposed by Pliszka (1992) and that there might be a different relationship between anxiety and impulsivity than is known [62].

## Diagnostic Challenges

The comorbidity of ADHD and anxiety disorders can lead to diagnostic challenges for a variety of reasons. According to Jarret and Ollendick (2008), co-existence of ADHD and anxiety disorders is a complex issue and becomes more complicated because of both methodological and substantive reasons [14]. The overlap between the symptoms of ADHD and anxiety disorders such as inattention, distractibility, difficulty in concentrating, irritability, psychomotor agitation or restlessness, and mood instability is one of the methodological problems that create diagnostic challenges [12••, 14, 23, 63, 64, 65•]. Subjective feelings and experiences may be similar both in patients with ADHD and anxiety, and it may not be possible to distinguish one from the other [23]. These overlapping symptoms may be easily misattributed to anxiety disorders rather than ADHD or vice versa and thus leading to misdiagnosis [65•].

For example, according to both DSM-IV and DSM-5, certain generalized anxiety disorder (GAD) symptoms such as restlessness, irritability, insomnia, and concentration problems overlap with ADHD diagnostic criteria [1, 66]. In relation to this topic, Tannock (2000) assumed that the presence of overlapping symptoms between these two disorders might increase the rates of comorbidity between ADHD and GAD. While worry or intrusive thoughts caused by anxiety can be manifested as attention deficit, restlessness or irritability caused by anxiety can be manifested as symptoms of hyperactivity or impulsivity [14, 31]. As a whole, these overlapping symptoms between ADHD and anxiety can pose serious challenges for making an accurate diagnosis of ADHD and anxiety, and this can cause difficulties in choosing appropriate treatment options [12••]. Therefore, clinicians should pay attention to distinguish the comorbid disorder when evaluating these overlapping symptoms.

Another methodological problem arising from the co-existence of ADHD and anxiety disorders is the inconsistencies in the definitions of the disorders and variation of diagnostic tools that are used in studies. Diagnostic criteria for both ADHD and anxiety disorders have changed over time from DSM-III-R to DSM-IV, even to DSM-5 [14, 66]. For example, subtypes of anxiety disorders section in the DSM-IV have changed in DSM-5. Obsessive–compulsive disorders and post-traumatic stress disorder were excluded and defined as separate disorders [1, 66]. Moreover, selective mutism and separation anxiety can be also diagnosed in adult patients [66]. As a result, it can be said that studies

with different definitions and classifications have led to variable results that are inconsistent with each other and thus, this situation can result in interpreting the data with difficulty.

The differences in the content of the diagnostic tools are also a problem. For example, DSM-IV SCID-I, which is widely used for the diagnosis of anxiety disorders, may play an important role in underestimating ADHD comorbidity in patients with anxiety disorders, since it does not contain an ADHD section [35, 42]. According to Pliszka (2019), diagnostic methods have been rarely discussed in the studies on the comorbidity of anxiety and ADHD [25]. Some of the studies have assessed the parent and child separately using a well-structured interview or rating scales, whereas others have been used a semi-structured diagnostic interview combining clinical examination and parent–child report [25]. He suggests that it is essential to keep these differences in mind so that not to misinterpret the studies when comparing them. Given this information, the choice of the diagnostic tools and differences in definitions of the disorders may also lead to diagnostic challenges.

Furthermore, according to Jarrett and Ollendick (2008), nosological and descriptive problems may complicate the informant effects or biases and cause diagnostic difficulties. In recent years, most of the studies have been applied by using multi-informant reports such as child, parents, and teachers to diagnose disorders [14]. Information obtained from these multiple sources may be inconsistent with each other due to halo effects on informants [14], because it was reported that informants may underestimate or overestimate symptoms of these comorbidities [67]. Moreover, the investigator's experience and interviewing style may also affect the diagnosis status and the same child may or may not be diagnosed [25]. It may be useful to apply combinatorial strategies to obtain the influences of these various factors on comorbidity findings [68]. Some authors suggest that several statistical analyses including confirmatory factor analysis and structural equation modeling are used to eliminate random error when assessing child behavior by applying parent and teacher measures and thus, one way of regarding such biases might be comparing the objective behavior of a child with ratings of multiple informants [14, 69].

Another diagnostic challenge in comorbidity of ADHD and anxiety disorders is that the clinical manifestation of ADHD changes with increasing age. As the age of patients with ADHD increases, the hyperactivity component may incline to decrease whereas attention deficit may become stable [9, 70]. According to Krone and Newcorn (2015), there are three main reasons for increased ADHD and anxiety co-existence in adolescence [64]. First, because of increased maladaptive behaviors, performance problems, and ADHD-related failures, inherently activated developmental stressors may trigger increased anxiety symptoms.

Second, when psychomotor activity decreases, diagnosis may become more difficult, as attention deficit is less evident and easily confused with anxiety symptoms. Finally, the presence of comorbidity with other disorders (such as ADHD) may appear more likely, since the frequency of anxiety disorders also increases with age [64]. Considering inattention symptoms related to anxiety disorders subtypes [27], anxiety may become manifest in clinical practice [23]. Since it is difficult to differentiate whether primary anxiety or secondary anxiety is caused by ADHD symptomatology [12], follow-up studies are needed to investigate this complex relationship.

## Treatment Challenges

Due to the ongoing debate about the etiology, psychopathology, and diagnostic features of the association between ADHD and anxiety disorders, choosing the appropriate treatment option emerges as another challenge. The answers to the following three questions on this issue are important. First, how does the presence of anxiety affect the response to ADHD medication (mainly stimulants) in patients with ADHD? Second, does stimulant therapy increase or decrease existing anxiety? Lastly, which treatment strategy should be chosen for anxiety and ADHD co-occurrence?

There are studies investigating how the presence of anxiety affects treatment outcomes in patients with ADHD (Table 1). As mentioned above, some studies have reported that the presence of anxiety reduces the methylphenidate (MPH) response in patients with ADHD [47–49, 71–73]. Buitelaar et al. (1995) indicated that the presence of low anxiety rates was one of the predictors of a strong MPH response [72]. In one study conducted with 267 children aged between 6 and 12 years, Ter-Stepanian et al. (2010) reported that ADHD and comorbid anxiety patients were more likely to have poor treatment response regardless of age, gender, or socioeconomic status [73]. However, other studies did not support these results and indicated that the presence of anxiety did not affect the MPH response [13, 74–76] (Table 1).

There is still an uncertainty regarding the answer to the question “does stimulant treatment increase or decrease anxiety?,” because anxiety is evaluated as a side effect of both MPH and amphetamine-derived medications in patients with ADHD [77]. Moreover, the US Food and Drug Administration warned against the increasing risk of anxiety due to ADHD medications [12]. On the contrary, increasing number of studies have reported that ADHD medications (stimulant or non-stimulant drugs) reduce or improve accompanying anxiety symptoms [50–57, 78] (Table 2).

In a meta-analysis, Coughlin et al. (2015) demonstrated that psychostimulant treatments diminish anxiety risks in

**Table 1** Studies examining whether the effects of comorbid anxiety on psychostimulants response

Reference	N	Subjects	Design	Key findings
Piszka (1989) [47]	43	Children who met DSM-III-R criteria for ADHD	A double-blind trial of MPH	Patients with ADHD + anxiety had worse response to the MPH than patients with ADHD without anxiety
Tannock et al. (1995) [49]	40	Anxious ( $n = 18$ ) and non-anxious ( $n = 22$ ) children with ADHD	A randomized, double-blind, placebo-controlled, crossover trial of MPH	The presence of comorbid anxiety in patients with ADHD anticipates a less robust response to MPH
DuPaul et al. (1994) [71]	40	Children with ADHD	3 doses of MPH (5, 10, 15 mg) were assessed in a double-blind, placebo-controlled trial	Children with ADHD with internalizing disorder are less expected to respond to MPH
Buitelaar et al. (1995) [72]		Children with ADHD	A double-blind, placebo-controlled trial of MPH	Prevalence rates of low anxiety is one of the strong predictor of MPH response
Ter-Stepanian et al. (2010) [73]	267	6–12-year-old children with ADHD	A double-blind, placebo-controlled, 2-weeks of MPH trial	Poor response in children with ADHD + anxiety after controlling for age, sex, and socioeconomic status
Diamond et al. (1999) [74]	91	Children with ADHD	A randomized, placebo-controlled, a dose of 0.7 mg/kg MPH	There were no distinguishing response to MPH between ADHD with anxiety group and ADHD without anxiety group
MTA (1999) [13]	579	Children with ADHD	Medication, behavioral and combination treatment or 14 months of community care treatment	The presence of comorbid anxiety disorder is not associated with poor response to medication management
Garcia et al. (2009) [75]	280	Children and adolescent with ADHD	A naturalistic study: MPH monotherapy in patients with ADHD with and without comorbid anxiety	The presence of comorbid anxiety does not affect the response to MPH
Blouin et al. (2010) [76]	18	Pediatric patients with ADHD	Small pilot study: 4–6 weeks following study	The presence of anxiety does not affect behavioral response to MPH in patients with ADHD
Coughlin et al. (2015) (a meta-analysis) [77]	2959	Children with ADHD	A meta-analysis: twenty-three studies, including 2959 children with ADHD	When compared to placebo, taking higher doses of stimulants were related to a decreased emergence risk of anxiety response to psychostimulants

ADHD attention deficit/hyperactivity disorder, MPH methylphenidate

**Table 2** Studies investigating the effectiveness of ADHD medications in patients with ADHD and comorbid anxiety disorders

Reference	N	Subjects	Design	Key findings
Summer et al. (2006) [50]	176	Patients with ADHD and comorbid anxiety disorders (such as separation anxiety, or SAD) (based on DSM-IV criteria)	A randomized, double-blind, multicenter trial, 12 weeks of ATX ( <i>n</i> = 87) or placebo ( <i>n</i> = 89)	ATX is found effective in pediatric patients with ADHD + anxiety
Geller et al. (2007) [51]	113	Ages 8–17 years, patients with ADHD and comorbid GAD/ separation anxiety disorder, and/or SAD (based on DSM-IV criteria)	A randomized, double-blind, 12 weeks of ATX ( <i>n</i> = 55) or placebo ( <i>n</i> = 58)	ATX was efficacious in reducing both ADHD and anxiety symptoms in patients with ADHD with comorbid anxiety
Adler et al. (2009) [52]	442	Adults patients with ADHD and comorbid SAD	A randomized, double-blind, placebo-controlled, 40–100 mg ATX ( <i>n</i> = 224) or placebo ( <i>n</i> = 218)	ATX is effective in terms of improvement of ADHD and SAD symptoms in adults
Young et al. (2011) [80]	502	Patients with ADHD	A randomized, double-blind, placebo-controlled, 60–100 mg ATX ( <i>n</i> = 268) or placebo ( <i>n</i> = 234)	There were no important differences in terms of depressive and anxiety scores in both groups
Durell et al. (2013) [81]	445	Adult patients (18–30 years old) with ADHD	A randomized, double-blind, ATX treatment ( <i>n</i> = 220) or placebo ( <i>n</i> = 225)	When compared with placebo, ATX monotherapy diminished ADHD symptoms and makes improvement on executive functioning deficits
Golubchick et al. (2014) [53]	21	Patients (8–18 years old) with ADHD with comorbid SAD	12 weeks of MPH treatment	MPH was associated with a significant reduction in both ADHD and SAD scores
Bloch et al. (2015) [79]	61	Patients with ADHD ( <i>n</i> = 36) and control group ( <i>n</i> = 25)	Used state anxiety test and cognitive performance test, MPH treatment	MPH reduced state anxiety in patients with ADHD, but did not reduce in control group
Hutchinson et al. (2016) (a review) [56]		Patients with ADHD and comorbid conditions	14 randomized controlled trials ( <i>n</i> = 1348 ATX, and <i>n</i> = 832 placebo)	ATX was found effective for decreasing the symptoms in patients with ADHD with comorbid anxiety
Scirmova et al. (2016) [57]	69	Patients with ADHD and comorbid anxiety	ATX treatment ( <i>n</i> = 36) MPH treatment ( <i>n</i> = 33)	Both ATX and MPH are effective in reducing both ADHD and anxiety symptoms. ATX was more effective in decreasing anxiety symptoms, compared to MPH
Koyuncu et al. (2017) [55]	20	Adult patients with SAD and comorbid ADHD	Retrospective case series	MPH monotherapy was effectively improved both ADHD and anxiety symptoms
Clemow et al. (2017) [78] (A review)		A review about the effect of ATX treatment	A total of 50 clinical studies (37 in children; 13 in adults)	There are studies found that ATX was effective in reducing both ADHD and anxiety symptoms

ADHD attention deficit/hyperactivity disorder, SAD social anxiety disorder, GAD generalized anxiety disorder, MPH methylphenidate, ATX atomoxetine

children with ADHD compared to placebo [77]. They suggested that increasing anxiety symptoms are probably incidental rather than stemming from psychostimulants during treatment. According to these authors, there may be two explanations for relieving anxiety with stimulant therapy in ADHD patients: First, stimulant drugs have a direct effect in reducing anxiety. Second, stimulants diminish anxiety indirectly by treating maladaptive behaviors that resulted from ADHD symptoms [77].

Bloch et al. (2013) found that both state anxiety and cognitive performances were elevated in adult patients with ADHD who receive MPH, but state anxiety did not diminish while taking MPH in the control group [79]. Additionally, Atomoxetine (ATX, non-stimulant drug) was found to be more effective than placebo in reducing both ADHD and anxiety symptoms [50–52, 56, 78]. Snircova et al. (2016) reported that both ATX and MPH were effective in reducing ADHD symptoms, but ATX was more effective in reducing accompanying anxiety in children and adolescents [57]. On the other hand, in a randomized, double-blind, placebo-controlled study, there were no important differences in terms of depressive and anxiety scores in ATX and placebo groups [80]. Durell et al. (2013) found that ATX was more effective than placebo in improving ADHD symptoms, yet it was not effective in reducing anxiety in adult patients with ADHD and anxiety [81].

There are also studies evaluating the effectiveness of simultaneous use of antidepressant and ADHD treatment in patients with ADHD and comorbid anxiety disorders. In a study, fluvoxamine and placebo were added for 8 weeks to patients whose ADHD symptoms but not comorbid anxiety improved with MPH monotherapy [82]. They found that there was no significant difference between MPH + fluvoxamine and MPH + placebo groups in terms of recovery from anxiety [82]. Kratochvil et al. (2005) stated that ATX monotherapy was effective in treating ADHD as well as anxiety and depressive symptoms in patients with ADHD and accompanying depression or anxiety [83]. However, the recovery of the ATX + fluoxetine group was not significantly different from the ATX + placebo group [83]. In another study involving thirty-two adult patients with ADHD plus anxiety disorder, who are resistant to antidepressants, the mixed amphetamine salt was added to treatment and it was reported that there were robust reductions in both ADHD and anxiety symptoms scores [84]. The results of the combination studies do not sufficiently support the conclusion that they provide more benefit than monotherapy [23]. Moreover, bupropion monotherapy, which is recommended as the second-line therapy in ADHD, did not differ from placebo in reducing both depression and anxiety scores in patients with ADHD [85].

In the light of the abovementioned literature, various perspectives have been stated about which treatment options

should be preferred in patients with ADHD and anxiety as well as which strategy should be followed during the treatment process. According to Weiss et al. (2011), ADHD and anxiety are dissimilar; however, they exacerbate each other when they occur together [23]. When clinicians encounter with this comorbidity, both disorders should be evaluated independently and addressed with determination [23, 25••].

Kooij et al. (2019) published a treatment strategy for comorbidity conditions (Updated European Consensus Statement on diagnosis and treatment of adult ADHD) [86••]. They proposed that the most severe disorder should be treated first with pharmacological treatment. According to this consensus statement, moderate mood or anxiety disorders may respond to ADHD treatment and they can be treated simultaneously [86••]. The presence of anxiety in patients with ADHD should not be considered an obstacle for psychostimulant treatment [25••]. According to Pallanti and Salerno (2020), psychostimulant drugs should be titrated slowly at the beginning of treatment because of the potential risk of increasing anxiety. If a patient cannot tolerate the stimulant therapy, it should be switched to ATX [12••].

Although the advantage of combining ADHD medications with antidepressants such as specific serotonin reuptake inhibitors (SSRIs) against monotherapy has not been adequately studied [23], the combination strategy might be an option in some cases [25••]. Moreover, cognitive-behavioral therapy (CBT) may be another alternative, although it has not been studied extensively in ADHD and comorbid anxiety patients [25••, 87]. In the MTA Study (1999), children who had ADHD with comorbid anxiety improved effectively through behavioral therapy and pharmacological treatment [13].

On the contrary, in the case of this comorbidity, strategies that prioritize the treatment of anxiety disorders (SSRI and/or CBT) may also be preferred. If ADHD symptoms do not improve, the ADHD medication may be added [25••].

## Conclusion

High rates of comorbidity between ADHD and anxiety disorders have been reported in both childhood and adulthood studies. The results of these studies have supported a complex relationship between the two disorders. ADHD and anxiety affect each other and one disorder may cause another. The close relationship between the two disorders and the presence of overlapping symptoms are likely to cause diagnostic and therapeutic difficulties.

First, overlapping symptoms of ADHD and anxiety including psychomotor agitation, restlessness, inattention, difficulty concentrating can create serious diagnostic challenges of ADHD and anxiety disorders. Therefore, clinicians should be careful distinguishing the two disorders



when faced with these overlapping symptoms to avoid misdiagnosis.

Second, changes in definitions of disorders (for example, age of onset of ADHD in DSM-5 is up to 12 years old) or in disorder groups over time (for example, OCD separated from anxiety disorders in DSM-5) can lead to inconsistent results and difficulties in interpreting studies. Third, differences in the content of diagnostic tools used in studies may also lead to serious problems. Fourth, informative effects (such as multiple sources of information and biases) and investigator's experience and interrogating style may also affect the diagnosis or and cause diagnostic challenges. Lastly, the clinical picture of ADHD changes with age. Since the attention deficit component tends to be more permanent, symptoms of anxiety may become more pronounced in adulthood. Moreover, as other anxiety disorders also begin at this age, it can become more difficult to distinguish whether the current anxiety is primary or secondary to ADHD symptoms.

In treatment, although earlier studies reported that the presence of anxiety reduced the response to psychostimulants, recent studies support the idea that it does not change the response to psychostimulants. There are an increasing number of studies showing that both stimulant and non-stimulant ADHD treatments also treat concurrent anxiety in ADHD + anxiety patients. When patients with ADHD and comorbid anxiety are evaluated in clinical practice, both disorders should be considered and treated separately. Among them, the most severe one should be treated first with pharmacological treatment. If comorbid anxiety symptoms improve with ADHD treatment, treatment can be continued in this way. However, if it is not sufficient, antidepressants and CBT can be added to stimulant and non-stimulant therapies.

## Future Directions

There are several issues that need to be addressed in the future. The comorbidity of ADHD and anxiety disorders can easily cause misdiagnosis due to the subjective nature of overlapping symptoms [64]. Moreover, continuous changes in the diagnostic criteria and classification of ADHD and anxiety disorders may also lead to inconsistent results. As well as informant effects, the differences in the content of diagnostic tools and non-standardization arise as a complex problem [14]. In order to overcome these problems, a novel methodology, standardized interview tools, and new statistical analysis methods are needed to define more clearly the phenotype of this co-occurrence which will lead to advances in behavioral and molecular genetics [14].

As the prevalence of this comorbidity increases with age, it is important to understand the effects of it on symptom severity. It is important to reveal the developmental nature of

this comorbidity with future follow-up studies. These follow-up studies are likely to explain the etiology and underlying neurobiological basis, and pave the way for more effective treatment approaches in the future [64].

In addition, studies are needed to show whether ADHD and accompanying anxiety disorders are related. Might an anxiety disorder develop secondary to ADHD? How can we distinguish between primary and secondary anxiety? In a 10 years follow-up study, patients with ADHD who take psychostimulant treatment have lower rates of subsequent depression and anxiety disorders than patients with ADHD who do not receive the treatment [58]. Does early diagnosis and treatment of ADHD prevent later anxiety disorders? Follow-up studies are needed to investigate the developmental aspects of ADHD and anxiety.

Finally, there are still many unanswered questions regarding the treatment of these comorbidities. How should the treatment be in case of comorbidity? What is the first choice treatment option? Should we choose monotherapy or initiate separate treatment for both disorders at the same time? Is CBT a preferable option? On the other hand, psychoeducation might be important for being aware of ADHD symptoms and for managing maladaptive behaviors caused by ADHD symptoms. CBT might be helpful in reducing both ADHD and anxiety symptoms. Studies with larger sample sizes are needed to explain this complicated topic in a comprehensive way.

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