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A Review of Co-Morbid Depression in Pediatric ADHD: Etiologies, Phenomenology, and Treatment

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Abstract

This paper reviews the literature and highlights the need for further research regarding the phenomenology, etiology, assessment, and treatment of co-morbid depression in patients with attention-deficit/hyperactivity disorders (ADHD). Depression occurs in youths with ADHD at a significantly higher rate than in youths without ADHD. Youths with ADHD and depression together have a more severe course of psychopathology and a higher risk of long-term impairment and suicide than youths with either disorder alone. Assessment of such co-morbid depression is complicated by overlapping symptoms with ADHD and with other disorders that commonly occur with ADHD. Depressive disorders typically emerge several years after the onset of ADHD and may arise from environmental difficulties associated with chronic ADHD that interact with genetic risks as the child gets older. Despite a scarcity of well-designed treatment studies for youths with ADHD and co-morbid depression, there is increasing preliminary evidence for the role of stimulants, selective serotonergic reuptake inhibitors, bupropion, and atomoxetine to target either or both disorders. There is also some indirect evidence for the benefit of combining pharmacological treatments with psychosocial interventions that specifically target relevant environmental factors and functional impairments.

Prevalence and Morbidity

Attention-deficit/hyperactivity disorder (ADHD) occurs in roughly 3–5% of all children and adolescents (Cantwell 1996), whereas major depressive disorder (MDD) occurs in roughly 2% of children and 8% of adolescents (Birmaher et al. 1996). A review of studies in community samples has reported that the rate of MDD in youths with ADHD is 5.5 times higher than in youths without ADHD, with rates ranging from 12% to 50% (Angold et al. 1999). Co-morbid depression in youths with ADHD occurs in clinical samples at even higher rates than in community samples (Pliszka 1998; Spencer et al. 1999).

The increased rate of co-morbid depression in ADHD youths is not an artifact of rater biases, overlapping symptoms, or other methodological artifacts (Biederman et al. 1995; Milberger et al. 1995; Biederman et al. 1996; Angold et al. 1999), but may be an epiphenomenal effect related to co-morbid disorders that occur widely in youths with ADHD (e.g., anxiety disorders, oppositional defiant disorders, or conduct disorders) (Angold et al. 1999; Burke et al. 2005). However, at least one study in a community sample has reported a higher rate of depression in youths with ADHD than in youths without ADHD, independent of other co-morbidity (Blackman et al. 2005). Depressive disorders in youths with ADHD typically occur several years after the onset of ADHD (Kovacs et al. 1994; Biederman et al. 1995). A common notion is that the cumulative effects of ADHD-related impairments and the negative environmental circumstances triggered by these may lead some youths with ADHD to eventually develop depression (Waxmonsky 2003; Blackman et al. 2005; Ostrander et al. 2006; Herman et al. 2007).

Depression or ADHD occurring alone in childhood is associated with substantial long-term impairment, morbidity, and an increased risk of suicide (Birmaher et al. 1996; Cantwell 1996; James et al. 2004). However, youths with ADHD and depression occurring together display even greater levels of psychosocial impairment than youths with either ADHD or depression alone (Rohde et al. 1991; Rohde et al. 2001; Blackman et al. 2005; Daviss et al. 2006b; Biederman et al. 2008). Female patients with both depression and co-morbid ADHD have earlier ages of onset of depression,

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longer durations of depressive episodes, and higher rates of suicidality and hospitalizations than those with depression alone (Biederman et al. 2008). After successful treatment for their depression, patients with co-morbid ADHD and depression have higher rates of depressive recurrence than those with depression alone (Rohde et al. 2001). Adult patients with co-morbid depression and ADHD have substantially higher overall health-care costs than those with depression only (Fishman et al. 2007). Clearly, the co-morbid occurrence of ADHD and depression is a significant public health problem for youths and adults.

Etiology

Studies have looked specifically at the role of ADHD severity and impairment as potential risk factors for later depression with mixed findings. A recent series of cross-sectional and longitudinal studies has suggested various pathways in youths with ADHD may account for the development of co-morbid depression (Ostrander et al. 2006; Ostrander and Herman 2006; Herman et al. 2007). Early ADHD symptoms lead to problems with academic functioning (Herman et al. 2007), social relationships (Ostrander et al. 2006), and parental interactions (Ostrander and Herman 2006) that may directly or indirectly contribute to episodes of depression in a subset of youths with ADHD. This suggests that early interventions to improve social and family interactions and competence in school may prevent or treat co-morbid depression in ADHD youths.

Other investigators have failed to find an association between the severity of ADHD symptoms and the risk or course of depressive disorders. One longitudinal study reported that persistence of MDD episodes in youths with ADHD was independent of ADHD-related impairment and indices of school dysfunction, and concluded that such co-morbid depression should not be downplayed as simply ADHD-related demoralization (Biederman et al. 1998). Two cross-sectional studies have also failed to show an independent link between variables of ADHD severity and depressive symptoms (Drabick et al. 2006) or lifetime depressive episodes (Daviss et al. 2006b).

Other individual risk factors for depression in children and adolescents in general include female sex and co-morbid anxiety and oppositional and conduct disorders (Birmaher et al. 1996; Angold et al. 1999; Zalsman et al. 2006). Genetic factors may also account for the increased risk of depression in some youths with ADHD. Twin and adoption studies have indicated that ADHD is one of the most heritable psychiatric disorders, with estimates of heritability ranging from 75 to 91% (Thapar et al. 2005). The heritability of pediatric depressive disorders, especially in preadolescents, is lower than for ADHD, but genetic factors in adolescents may play at least a moderate, indirect role through interactions with environmental factors (Rice et al. 2002). A review of relevant family and population studies of ADHD and depression suggests a familial link between ADHD and depression, particularly in families having antisocial disorders (Faraone and Biederman 1997). The conclusion of this review was that although ADHD and MDD share common familial risk factors, differences between ADHD patients with and without depression are likely due to environmental rather than genetic effects (Faraone and Biederman 1997).

General environmental risk factors for pediatric depression may include exposure to traumatic life events, adverse family environments, poor parental and peer relationships, and family conflict (Birmaher et al. 1996; Zalsman et al. 2006). Such environmental risks have not been well studied in youths with ADHD. Only one study has examined environmental risk factors prospectively for subsequent depression specifically in youths with ADHD, reporting that family conflict was not an independent predictor of co-morbid MDD in adolescent females with ADHD (Biederman et al. 2008). Another longitudinal study reported that interpersonal deficits but not adverse family environments were predictive of depressive persistence in youths with co-morbid ADHD and MDD (Biederman et al. 1998). A retrospective study reported that adolescents with ADHD and lifetime histories of depression had higher levels of family conflict, negative life events, and trauma exposure compared to never-depressed ADHD controls, even after controlling for difference in co-morbidity and demographic variables (Daviss et al. 2006b). Another cross-sectional study reported that adverse family environments, poor parenting behaviors, and poor peer relationships in ADHD children were independent predictors of depressive symptoms (Drabick et al. 2006). Given the cross-sectional designs of these last two studies, it is unclear whether such environmental correlates in these studies are causes or effects of co-morbid depression.

Another environmental factor potentially related to depressive risk in youths with ADHD is pharmacotherapy for ADHD. Stimulant medications are the most widely used medications for ADHD and may occasionally cause dysphoric or labile moods (Wilens and Spencer 2000). Two animal studies in juvenile rodents have raised concern that early stimulant exposure may increase the risk of developing co-morbid depression (Bolanos et al. 2003; Carlezon et al. 2003). A recent case-control, retrospective study of adolescents with ADHD used survival analyses to examine whether time from the onset of ADHD until first pharmacological treatment influenced the long-term risk of co-morbid MDD (Daviss et al. 2008). Greater latency of first pharmacotherapy for ADHD was the strongest single predictor of MDD onset, and this link persisted independent of the subjects' trauma exposure, suggesting that earlier ADHD pharmacotherapy may have a protective effect. However, the authors noted the potential confounding effect of female sex and did not examine other familial and parental factors that might also explain delays in first pharmacotherapy (Daviss et al. 2008).

Assessment

Accurate assessment of pediatric depression and other co-morbid disorders generally requires both child and parent reports (Birmaher et al. 2007). Several well-validated measures of depressive and anxiety symptoms are useful in this regard (Myers and Winters 2002). The clinician must also screen for co-morbid externalizing and anxiety disorders, as well as substance and alcohol use disorders, and signs of medical problems that can mimic depressive symptoms. An assessment for suicide risk should include asking about past and current suicidal thoughts and behaviors and the child's access to potential means of suicide, such as guns at home.

Consideration of adverse environmental factors and areas of dysfunction may help identify possible etiological factors and targets for intervention. Careful review of the child's previous pharmacological and nonpharmacological treatments and of school assessments and interventions may also be useful. Finally, the clinician should ask about family members' history of mental health problems and their responses to treatments, which may guide not only diagnosis but also treatment of the child.

In youths with ADHD, a diagnosis of depression is further complicated by multiple symptoms that overlap between the two disorders or with other childhood psychiatric disorders (Milberger et al. 1995; Diler et al. 2007). Medications used to treat ADHD may cause side effects like insomnia or decreased appetite that mimic vegetative symptoms of depression (Pliszka et al. 1999). A recent study reported that symptoms that best differentiate ADHD youths with and without co-morbid MDD are social withdrawal, anhedonia, depressive cognitions, suicidal thoughts, and psychomotor retardation, whereas irritability, concentration problems, and most other vegetative symptoms do not (Diler et al. 2007). Not surprisingly, total scores on even well-validated depressive measures are less accurate when screening for MDD among children with ADHD (Myers and Winters 2002; Daviss et al. 2006a; Daviss et al. 2007).

Both parents and children may offer valid but discrepant information about children's depressive symptoms (Jensen et al. 1999). Parents are typically more accurate regarding the temporal course of depressive symptoms (Kovacs 1986), and, along with teachers, are better reporters regarding symptoms of ADHD, irritability, and externalizing disorders, whereas youths tend to be better reporters of depressive cognitions, suicidal thoughts, and anxiety symptoms, especially as they get older (Jensen et al. 1999). Youths with ADHD may overestimate their social and other competencies (Hoza et al. 1993; Hoza et al. 2000), and symptoms of distractibility, carelessness, and impulsivity may make them less accurate in reporting depressive symptoms. On the other hand, parents of ADHD youths may confuse symptoms of depression with symptoms of other co-morbidity (Daviss et al. 2006a; Diler et al. 2007), and may be biased by their own mental health problems in reporting their child's symptoms (Jensen et al. 1999; Birmaher et al. 2007). As such, the clinician must carefully weigh all available sources of clinical data and observe the child during the interview for signs of depression and other disorders to arrive at a "best estimate" of the child's current diagnoses (Birmaher et al. 2007).

Sometimes the presenting complaint in older patients is a recent history of mood symptoms, while a review of symptoms suggests a chronic history of inattention or hyperactive/impulsive symptoms that preceded the onset of the mood disorder (Alpert et al. 1996). Whereas onset of symptoms before the age of 7 years old is a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criterion for ADHD, the DSM-IV field trials have suggested that youths with the inattentive subtype of ADHD in particular may not always have such an obvious early age of onset and yet be just as symptomatic and impaired (Applegate et al. 1997). Accordingly, some experts have argued for a more lenient age-of-onset criterion in youths with ADHD (Barkley and Biederman 1997). As such, a provisional diagnosis of co-morbid ADHD might also be considered and targeted with pharmacotherapy when ADHD symptoms persist after a depressive episode has resolved.

Another critical issue is the need to screen carefully for a history of manic or hypomanic symptoms. The rate of bipolar disorders in youths with ADHD in clinical settings is as high as 23% based on studies of two distinct samples (Wozniak et al. 1995; Biederman et al. 1996). Likewise, in youths with depressive disorders, the rate of later developing a bipolar disorder is 20–40% (Strober and Carlson 1982; Geller et al. 1994). Classic symptoms of childhood bipolar disorders include severe elation or irritability, grandiose or racing thoughts, age-inappropriate levels of sexual interest, and decreased need for sleep. Other nonspecific signs and symptoms may include psychotic symptoms, pharmacologically induced mania/hypomania, severe aggressive outbursts, early onset of mood symptoms, and a family history of bipolar disorder (Strober and Carlson 1982; Geller et al. 1994; Pliszka and AACAP-Work-Group-on-Quality-Issues 2007). The clinician should review and continue to monitor for these signs of bipolarity after initiating any pharmacotherapy for ADHD or depression.

Treatment

Assuming a proper diagnosis of ADHD and co-morbid depression has been made, the clinician should use a biopsychosocial approach to offer individualized treatments that target specific functional deficits in the patient as well as environmental factors likely to be contributing to the child's psychopathology. More complicated cases will often require a broader array of pharmacological and psychosocial interventions.

Pharmacotherapy

Stimulants pharmacotherapy is generally considered the first-line treatment for uncomplicated ADHD, and there is also good evidence for the efficacy of atomoxetine, tricyclic antidepressants, and bupropion in such youths (Pliszka and AACAP-Work-Group-on-Quality-Issues 2007). A randomized controlled trial (RCT) of desipramine versus placebo in youths with ADHD has suggested that co-morbid depression may predict a better ADHD response to desipramine (Biederman et al. 1993). However, tricyclic antidepressants are rarely used today because of their cardiovascular risks, need for plasma level and electrocardiogram (ECG) monitoring, and lack of efficacy for pediatric depression in multiple RCTs (Hazell 1996). Findings from the Multimodal Treatment Study of ADHD (MTA) have suggested that children with co-morbid ADHD and anxiety are responsive to stimulant pharmacotherapy (MTA-Cooperative-Group 1999), but it is unclear how these findings relate to youths with ADHD and co-morbid depressive disorders. Two RCTs of ADHD youths with co-morbid anxiety or depressive symptoms have yielded contradictory findings regarding whether internalizing symptoms lessen response to methylphenidate (DuPaul et al. 1994; Gadow et al. 2002). No study to date has directly compared treatment responses in ADHD youths with and without depression. Thus, it is still not clear how co-morbid depressive disorders impact the response of children with ADHD to pharmacological treatments of their ADHD.

There is increasing evidence for the efficacy of selective serotoninergic reuptake inhibitors (SSRIs) in treating pediatric MDD in general (Cheung et al. 2006; Birmaher et al. 2007). Investigators in several recent trials of SSRIs in youths with MDD have conducted post hoc analyses of the effects of co-morbid ADHD on depressive response, once again with contradictory findings (Emslie et al. 1997; Birmaher et al. 2000; Keller et al. 2001; Emslie et al. 2002). The Treatment of Adolescent Depression Study (TADS) reported that co-morbid disorders were a significant moderator of lowered antidepressant response, but did not specifically report on the moderating effects of co-morbid ADHD (Curry et al. 2006).

To date, a few studies have examined the effects of pharmacological treatments, specifically in youths with both depressive disorders or symptoms and ADHD, as summarized in Table 1 below. Most studies are limited by their small sample sizes, and lack of placebo arms or randomized controlled designs, but provide preliminary evidence that monotherapy with bupropion, or combination therapies with stimulants, SSRIs, and atomoxetine may be reasonable alternative treatments for ADHD and co-morbid depression. Only one study of youths with ADHD and co-morbid MDD, a study of atomoxetine monotherapy, used a placebo-controlled design and showed significantly better improvement for ADHD, although not for depressive symptoms on active drug (Bangs et al. 2007). Although no subjects taking atomoxetine in this trial experienced emerging suicidality on active drug (Bangs et al. 2007), a recent change in the label of atomoxetine reports suicidality as a rare adverse event.

On the basis of the available empirical evidence, a consensus panel of experts in the Texas Children's Medication Algorithm Project (CMAP) recently revised their pharmacotherapy algorithms for ADHD and co-morbid depression (Pliszka et al. 2006; Hughes et al. 2007). These algorithms offer a rational approach to treating this co-morbid group. The CMAP panel recommends the use of validated depressive and ADHD instruments to monitor treatment response. They first recommend a single medication to target whichever is the more severe disorder, before resorting to medication combinations, because improvements in one disorder may coincide with improvements in the other. Changes in medications should be made one at a time. Regardless of the treatment selected, clinicians should educate families about the potential risk of worsening moods, suicidality, and iatrogenic mania and the need to monitor closely for such emerging problems. Clinicians should reconsider the child's underlying diagnoses and choices about treatment when adverse and unexpected responses to pharmacotherapy occur.

If ADHD is judged the bigger problem, the CMAP algorithm suggests an initial trial of a stimulant medication. Should the patient's depressive and ADHD symptoms persist on a stimulant alone, then the stimulant could be changed to an SSRI. If ADHD symptoms improve but not depressive symptoms, then a concomitant SSRI could be added. Alternatively, when the depressive disorder is judged the bigger problem, CMAP recommends consecutive trials of at least two separate SSRIs before resorting to bupropion or a tricyclic antidepressant as a third-line treatment. If ADHD symptoms persist despite improvement of depressive symptoms on an SSRI alone, then concomitant stimulant could be added (Pliszka et al. 2006; Hughes et al. 2007).

A recent study of the feasibility of the CMAP depression algorithm suggests that such an approach works reasonably well

Table 1. Pharmacological Trials Specifically of Youths with ADHD and Depression

Reference	n	*Subjects*	*Design*	*Key findings*
Gammon and Brown 1993	32	Youths with ADHD refractory to MPH; 25/32 had DD 6 also had MDD	12-week prospective study, with fluoxetine added and gradually titrated while MPH maintained	Adding fluoxetine helpful for both ADHD and depession in all subjects, and well tolerated.
Findling 1996	11	Adolescents and adults with MDD and ADHD whose depression had responded to SSRI monotherapy	SSRI maintained with MPH or Dex added	Combination of SSRI and stimulant was well tolerated and effective for residual ADHD
Daviss et al. 2001	24	Adolescents with ADHD and MDD or DD	2-week placebo run-in, followed by flexible dosing of bupropion SR for 8 weeks	Overall response rates of 88% for depression and 63% for ADHD; medication generally well tolerated
Kratochvil et al. 2005	173	Youths with ADHD and significant depressive or anxiety symptoms	8-week RCT with subjects assigned to ATX/PBO or ATX/fluoxetine	Both treatments well tolerated; both groups anxiety, depressive, and ADHD symptoms improved
Bangs et al. 2007	142	Adolescents with ADHD and MDD	9-week, placebo-controlled RCT of ATX	Subjects on ATX had greater improvement in ADHD ($p < 0.001$) but not depressive symptoms

ADHD = attention-deficit/hyperactivity disorder; MDD = major depressive disorder; DD = dysthymic disorder; RCT = randomized controlled trial; MPH = methylphenidate; Dex = dextroamphetamine; SR = sustained release; PBO = placebo; SSRI = serotonergic reuptake inhibitor; AE = adverse event; ATX = atomoxetine.

for co-morbid ADHD and depression in a community setting (Emslie et al. 2004). Of the 15 patients enrolled in the study with ADHD and a co-morbid depressive disorder, 9 were prescribed a stimulant first. Of these, only 2 had an SSRI added later for residual depressive symptoms. Another 2 initially received an SSRI alone, and 4 had the combination of an SSRI and a stimulant at entry into the study, with mixed success. This study provides preliminary evidence that these algorithms may be effective in treating ADHD and co-morbid depression, but that patients receiving treatment for ADHD and co-morbid depression need close follow up and may sometimes have to go beyond the first stage of the treatment algorithm.

Psychotherapy and other psychosocial interventions

There are several manualized psychotherapies now available for pediatric depressive disorders (Weersing and Brent 2006), with none having been studied specifically in youths with co-morbid ADHD and depression. However, two larger studies have shed some light on the potential benefits of combining pharmacotherapy and psychotherapy in groups with co-morbid disorders (MTA-Cooperative-Group 1999; March et al. 2004). In the MTA study, behavioral interventions were as effective as ADHD pharmacotherapy alone in treating youths with ADHD and co-morbid anxiety (MTA-Cooperative-Group 1999), and when ADHD and anxiety disorders occurred co-morbidly with externalizing disorders, combination therapies were superior. Once again, it is not clear whether such findings regarding psychosocial treatments would extend to ADHD youths with co-morbid depression. In TADS, cognitive behavioral therapy (CBT) performed no better than placebo in the overall sample, whereas both fluoxetine alone and fluoxetine in combination with CBT produced superior and consistent therapeutic effects for depression (March et al. 2004). Subsequent analyses suggested that youths with more severe and chronic symptoms, more co-morbidities, and greater impairment were less responsive overall but responded best on the combination of fluoxetine and CBT (Curry et al. 2006). There was also some suggestion that combination treatment lessened the risk of emergent suicidality associated with fluoxetine (Emslie et al. 2006). Taken together, findings from both the MTA and TADS suggest that more complex cases of co-morbid ADHD and/or depression may require more complex combinations of treatment.

Academic and social impairments in the school setting are widespread in youths with ADHD and depression and may be particularly important targets for psychosocial interventions. Many youths with ADHD alone are eligible for special accommodations based on Section 504 of the Rehabilitation Act. Youths with ADHD and co-morbid depression may require even more substantial remediation in school and be eligible for an Individualized Education Plan under the Individuals with Disabilities Education Act. It is important to discuss such options with patients and parents and encourage them to ask for an educational assessment and potential accommodations in school if the child appears eligible for these.

Conclusions and Future Research Directions

In summary, depressive disorders occurring in youths with ADHD, especially in clinical settings, are common, quite impairing, and pose special challenges with regard to proper assessment and treatment. There is increasing evidence to suggest that co-morbid depression in youths with ADHD results from a chronic history of functional deficits along with a mix of environmental and genetic factors. Despite the scarcity of well-designed treatment studies for youths with ADHD and co-morbid depression, there is preliminary evidence for the role of pharmacological treatments such as stimulants, SSRIs, bupropion, and atomoxetine to target either or both disorders. There is also some suggestion for the benefit of concomitant psychosocial interventions that target the child's functional deficits and relevant environmental factors, especially in more severe co-morbid cases. Clearly, further research is needed regarding the etiology, phenomenology, and treatment of youths with ADHD and co-morbid depression.

Disclosures

Dr. Daviss has served as a speaker for Quintiles CME, Inc, and as a paid co-investigator reviewing psychiatric assessments for Lexicor Inc.

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