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Comorbid Anxiety and Depressive Symptoms in Children and Adolescents: A Systematic Review and Analysis

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Abstract

Background.—A large and extensive body of research has examined comorbid anxiety and depression in adults. Children and adolescents also frequently present with comorbid anxiety and depression; however, research and treatment require unique environmental and neurodevelopmental considerations in children. As a result, our understanding of comorbid anxiety and depression in children and adolescents is limited.

Objective.—The goal of this systematic review was to examine current literature focused on comorbid anxiety and depression in children and adolescents. The review included theoretical conceptualizations as well as diagnostic, neurobiologic, prevention, and treatment considerations. In addition, a proposed algorithm for the treatment of comorbid anxiety and depression in children/adolescents is provided.

Methods.—This systematic literature review included three discrete searches in Ovid SP Medline, PsychInfo, and Pubmed.

Results.—The review included and synthesized 115 articles published between 1987 and 2015. The available evidence suggests that anxiety and depression are common in clinical populations of children and adolescents, and that comorbidity is likely underestimated in children and adolescents. Children and adolescents with comorbid anxiety and depression have unique presentations, greater symptom severity, and treatment resistance compared with those who have either disease in isolation. A dimensional approach may be necessary for the future development of diagnostic strategies and treatments for this population. Nascent neuroimaging work suggests that anxiety and depression each represents a distinct neurobiological phenotype.

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Conclusion.—The literature that is currently available suggests that comorbid anxiety and depression is a common presentation in children and adolescents. This diagnostic picture underscores the importance of comprehensive dimensional assessments and multimodal evidence-based approaches given high disease severity. Future research on the neurobiology and treatment of these common clinical conditions is warranted.

Keywords

anxiety; depression; child; adolescent; comorbidity

Depressive and anxiety symptoms frequently overlap in adults,[1,2] and an accumulating body of literature has substantiated their comorbidity across the adult lifespan. However, there is a dearth of evidence regarding the comorbidity and phenomenologic overlap of anxiety and depression in pediatric populations. Children and adolescents often present with distinct neuropsychiatric symptomatology that is compounded by unique environmental stressors and influenced by ongoing neurodevelopmental processes. These complex and dynamic factors warrant specific assessment and treatment considerations,[1] particularly since comorbidity of anxiety and depression in pediatric patients has received little attention.[1–6]

In this article, we systematically review and examine accumulating evidence related to comorbid anxiety and depressive symptoms in child and adolescent populations in order to 1) enhance theoretical conceptualizations of these disorders; 2) improve assessment and diagnosis, 3) enhance prevention and treatment strategies, and 4) guide future research. Moreover, with the recent release of the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5),[7] there are new changes to the psychiatric diagnostic conceptualization of the comorbidity of anxiety and depressive symptoms, especially with regard to subsyndromal symptomatology, which will be addressed here.

This systematic literature review was based on three independent searches using Ovid SP Medline (1948 to the present), PsychInfo (1806 to the present), and PubMed (1948 to the present), using the following terms: *anxious depression, child* (including *psychiatry* and *psychology*), *adolescent* (including *psychiatry* and *psychology*), *depressive disorder, anxiety disorder, depression comorbid anxiety,* and *mixed anxiety depression*. The search was limited to articles that were written in English and contained the following terms: *mixed anxiety depression, anxious depression, anxious mood, major depressive disorder (MDD) comorbid anxiety, child,* and *adolescent*. These searches resulted in a total of 115 articles included in this systematic review. These articles were published between 1987 and 2015 in the United States and the United Kingdom.

PREVALENCE OF COMORBIDITY

Anxiety and depression represent distinct disorders with specific clinical features, disease course, pathophysiology, and unique treatment strategies.[8] Anxiety and depression independently contribute to a significant proportion of the prevalence of mental health disorders. The World Health Organization (WHO) has identified depression as the leading cause of disability (as measured by years lived with a disability) and the second largest contributor to the global burden of disease (as measured by disability adjusted life years).[9]

Despite advances in mental health care, the WHO has noted that depression is currently the second largest contributor to global burden of disease among those 15–44 years of age for both sexes combined, and by 2020 will be the first contributor to global burden for all persons.[9] Anxiety disorders are presently the most common form of psychiatric illness in children and adolescents,[10–13] with annual prevalence rates that range from 5.7 to 17.7%.[14] Further, a significant proportion of anxious children will experience chronic courses of anxiety lasting through adulthood[14] and these individuals are at heightened risk for developing depressive disorders[15,16] (for review see Wehry et al 2015[17]). Consequently, the long-term effects of chronic anxiety symptoms include increased risk for additional anxiety disorders, MDD, illicit drug use, and poor academic performance.[18] In parallel, co-occurring depression and anxiety are commonly observed in epidemiologic samples, including in the National Comorbidity Survey (NCS).[19] In the NCS, 58% of patients (15 to 54 years of age) with MDD had a comorbid anxiety disorder.[19] The most frequent combinations involved MDD with comorbid generalized anxiety disorder (GAD) at 17.2% and with comorbid panic disorder at 9.9%.[19,20] Conversely, nearly a quarter of patients with an anxiety disorder may meet diagnostic criteria for comorbid depression.[19,20]

Comorbidity rates between depression and anxiety may be even higher in the child and adolescent populations. However, the diagnostic process in these populations is complicated by increased symptom severity and heterogeneous symptom presentations.[8] Biederman and colleagues observed that more than 95% of children with MDD had a comorbid diagnosis, with the highest rates for anxiety disorders.[4] Data suggest that single diagnoses in children and adolescents are rare, and that more individuals than not will have at minimum 2 psychiatric illnesses.[2,4–9,11–14,18–24] Comorbidity may increase symptom severity, predict worsening of global functional status (eg, poorer academic performance, increased familial conflict), increase substance abuse risk, and increase risk for suicide attempts.[21] Closer examination of the clinical presentation of comorbid anxiety and depression is necessary as comorbidity appears to be the rule rather than the exception in child and adolescent populations.

A DIMENSIONAL CONCEPTUALIZATION

As anxiety disorders co-occur with MDD at rates beyond what is explainable by chance alone, research suggests this may reflect a causal relationship.[1] Depression may precede anxiety, anxiety may precipitate depression, or both disorders may be the manifestation of a common etiopathology. In a study published in 1992 involving a population of adults (17 years of age and older), Coryell et al[1] observed that anxiety symptoms confined to an episode of primary depression were symptoms of that depressive disorder rather than being part of a separate disease. Furthermore, patients with primary depression who reported obsessions or compulsions, panic attacks, or phobias that were restricted to their current depressive episode were unlikely to develop these anxiety syndromes as autonomous disorders by the 5-year follow-up. Rather, they had an increased tendency to develop recurrent depressive episodes.[1] In addition, in that study, depressed patients with anxiety symptoms had poorer outcomes compared with those without anxiety symptoms. This would be expected if the symptoms were related to a comorbid anxiety disorder[1] as opposed to anxiety symptoms that reflect phenemologic overlap between depression and anxiety.

However, follow-up of these patients showed that they had no primary anxiety disorder,[1] which suggested that these comorbid anxiety syndromes were epiphenomenal features that predicted a more severe and persistent form of depression.[1]

Additional research has suggested that anxiety and depressive disorders should be grouped together as "distress" and measured along a continuum.[25,26] This dimensional conceptualization of anxiety and depression appears to more accurately depict the presentation of these disorders in child and adolescent populations. Using the Child Behavior Checklist (CBCL)[27] in pediatric patients, 4 to 18 years of age, Wadsworth et al[21] observed features consistent with the mixed anxiety/depressive syndrome and failed to find evidence for a distinct anxiety or depressive disorder. The results from Wadsworth et al reveal the presence of a continuum containing both affective and anxiety problems in children and adolescents.[21] These researchers argued that a dimensional conceptualization complements a categorical approach, as some children may fall at one end of the continuum displaying only symptoms of depression, while other children may fall at the opposite end of the continuum exhibiting only symptoms of anxiety.[21] The Wadsworth et al. study demonstrated that most children, however, appear to fall in the middle of the continuum, with problems of both anxiety and depression.[21] Their findings were consistent with earlier findings from Eaton et al,[22] who were unable to identify *pure* cases of depression devoid of anxiety symptoms. Therefore, whereas some children may exhibit symptoms that meet diagnostic threshold criteria for either a depressive or anxiety disorder, the symptoms in these areas that most children and adolescents exhibit are better explained as being on an affective/anxiety continuum.[17,18]

ANXIOUS-DEPRESSIVE SYMPTOMATOLOGY

Comorbid psychiatric diseases in general are associated with greater distress, increased disability, poorer response to treatment, and poorer prognosis.[26] Specific to comorbid anxiety and depression, complications include additional symptoms of negative self-evaluation, discouragement, and more severe depressed mood.[28] The anxious depressive symptomatology is comprised of additional psychiatric symptoms that include diurnal variation (with mood worse in the morning), somatic concerns (gastrointestinal symptoms, hypochondriasis), increased anergia, insomnia, agitation, poor concentration, depersonalization, subjective anger, obsessive thoughts and compulsive behaviors, distrustfulness, hypophagia, and lack of mood reactivity to changes in circumstances.[20,28]

Children and adolescent populations have similarly demonstrated greater disease severity when they present with coexisting anxiety and depressive symptoms.[18] Youth may also be more likely to present with increased somatic complaints compared with adult samples.[29–32] For example, Woodward and Ferguson[33] examined adolescent outpatients and determined that both anxiety and depression accentuated the reporting of somatic complaints. These somatic complaints often led to increased school avoidance and poorer academic performance.[33] Moreover, Woodward and Ferguson found that the presence of autonomic symptoms (eg, shakiness/trembling, flushes/chills, sweating, headaches) was most significantly associated with greater absence from school.[33] Somatic complaints and school refusal in this population are important to acknowledge, because poor school attendance

(especially when the result of anxiety and depressive symptoms) may lead to longitudinal academic difficulties and loss of peer relationships.[30] Findings from a study by Henker et al[13] that used electronic diaries in adolescents suggested that teenagers in the high anxiety group not only reported higher levels of anxiety and stress than those in the low anxiety group, but also experienced more depressive symptoms than those in the low anxiety group. Furthermore, anxious teenagers have been reported to disengage from socially constructive behaviors (eg, they have fewer conversations with friends, less participation in recreational activities) and to be more likely to engage in socially destructive behaviors (eg, increased smoking, increased isolation).[13]

The influence of the family milieu on child and adolescent symptomatology is also an important factor with regard to anxiety and depressive symptoms. Adolescents with high levels of anxiety symptoms report more family "chaos," less autonomy and openness, less intimacy/warmth in their families, and they are more likely to have controlling and overprotective parents.[32,34] In children and adolescents with MDD, depressive symptoms were linked with family disengagement.[32,34] One heritability study suggested that, through a reactive correlation between genotype and environment, anxious and depressed children may actually elicit a certain type of parenting style that is often more punitive and overbearing in nature, which in turn produces an environment that maintains or exacerbates anxious and depressive symptoms.[35] Targeting these family characteristics should be part of therapeutic treatment, which may improve family functioning and thereby decrease the severity and course of comorbid anxiety and depressive disorders.

NEUROBIOLOGICAL CORRELATES

To date, neuroimaging research has primarily focused on studies of pediatric depression or anxiety as opposed to comorbid conditions. However, common brain structures or neurocircuitry are often implicated in both disorders. In some but not all studies, adolescents with depression have demonstrated increased amygdala activity in the context of fearful stimuli when compared with healthy comparison groups.[36,37] Adolescents with MDD have also demonstrated hypoperfusion in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and amygdala when compared with healthy participants.[38] Other research has demonstrated increased striatal-dorsomedial prefrontal and striatal-ACC functional connectivity in adolescent subjects with MDD.[39] It should be noted that symptom severity was correlated with striatal and dorsomedial prefrontal functional connectivity in that study.[39] Neuroanatomical studies have demonstrated that depressed adolescents have decreased gray matter volumes in the caudate, DLPFC, ACC, and temporal lobe when compared with healthy subjects[40,41]

Parallel work in youth with anxiety implicates the prefrontal-amygdala network. This includes work demonstrating increased functional activity in the anterior cingulate cortex, [42,43] amygdala,[37,44] and ventrolateral prefrontal cortex.[37,45–47] Although results are not consistent, studies have also have observed neuroanatomical abnormalities in prefrontal-amygdala networks.[48–52] One group found increased right and overall amygdala volumes in pediatric patients with GAD.[48] Other studies have observed decreased left[50] and right[51] amygdala gray matter volumes in pediatric patients with a mixture of anxiety disorders.

Other groups have reported decreased anterior hippocampal gray matter volumes in anxious youth.[51] De Bellis and colleagues demonstrated that youth with GAD had increased gray and white matter volumes in the superior temporal gyrus.[49] A voxel-based morphometry study found increased gray matter volumes in the right precentral and right precuneus of adolescents with GAD compared with healthy controls. The patients with GAD also had lower gray matter volumes in the left orbitofrontal cortex and posterior cingulated.[52]

To date, little neuroimaging work has examined pediatric patients with anxiety and comorbid depression.[53] Studies in adults included a 2014 functional magnetic resonance imaging (fMRI) comparison of adults with MDD without anxiety, adults with MDD and panic disorder, and healthy subjects.[54] Adults with MDD displayed increased dorsal anterior cingulate cortex activation with reward anticipation, whereas the other groups did not.[54] A neurostructural study examined adults who had MDD with comorbid anxiety, adults with MDD only, and adults with anxiety only.[55] All 3 groups had decreased gray matter in the rostral anterior cingulate when compared with healthy controls but no differences were found among the patient groups.[55] Another neurostructural study of adults compared patients with MDD with anxiety symptoms, patients with MDD only, and healthy subjects.[56] Both patient groups had decreased gray matter in the superior parietal lobe. The patients with anxiety and comorbid depression had increased gray matter in the right temporal cortex.[56] Recently, Wehry and colleagues completed a voxel-based morphometry study comparing gray matter volumes among depressed adolescents without anxiety, depressed adolescents with comorbid anxiety, and healthy controls.[57] Adolescents with anxious depression had decreased gray matter in the right dorsolateral prefrontal cortex compared with depressed adolescents. However, compared with healthy adolescents, participants with anxiety and comorbid depression had increased gray matter in the pre- and post-central gyri. [57] Although evidence is nascent, youth with anxiety and comorbid depression may have distinct patterns of structural and functional abnormalities compared with youth with anxiety or depression alone. Further work could delineate more biologically oriented classification systems for clinical practice to assist with treatment selection.[57]

EFFECTS OF ANXIOUS DEPRESSIVE COMORBIDITY ON THE COURSE OF ILLNESS

While anecdotally some clinicians believe that depressed patients who experience comorbid anxiety and depressive symptoms present with a less severe course of depressive illness,[28] the preponderance of research suggests otherwise—that is, that patients with comorbid anxiety and depressive symptoms have more severe depression, a more chronic course of illness, and decreased response to treatment.[28,58,59] Furthermore, comorbid anxiety and depression is associated with increased rates of physical morbidity, cardiovascular disease, mortality, and likelihood of suicide relative to the rates of these conditions in isolation.[60] Anxiety symptoms also significantly predict family illness and course, as seen in Clayton et al.'s sample[28] of adults with primary depressive disorders who had high anxiety. The familial prevalence of primary depressive disorder was increased, and, when followed longitudinally over the course of 5 years, these individuals experienced poorer outcomes.

The increased risk for suicidal behaviors in this adult population is of critical concern. Cumulative lifetime prevalence estimates for suicide attempts in studies that assessed youth between the ages of 9 to 19 ranged from 3% to 7%, with the largest risk factors being mood, anxiety, disruptive, and substance use disorders.[61–69] Indeed comorbidity with an anxiety disorder is more common in suicidal youth, suggesting that comorbidity results in greater severity of the psychiatric illness and more functional burden.[61,62] The Great Smoky Mountains Study, published in 2006, prospectively evaluated 1420 youth (9–16 years of age) with anxiety disorders (specifically GAD) comorbid with depression and demonstrated an increased suicidal risk.[61] This raised the possibility that depression plus GAD represents a highly discriminating pattern of symptoms or other risk factors, as this was the only profile that independently predicted suicidality regardless of the severity of symptoms or impairment.[61] Similarly, in adults surveyed in the Netherlands Mental Health Survey and Incidences Study (NEMESIS),[62] the presence of an anxiety disorder was unequivocally associated with increased suicidal ideation and the co-occurrence of an anxiety disorder with MDD increased the likelihood of a suicide attempt. Psychological autopsy studies have reported that most completed suicides occur on the first suicide attempt, thus children and adolescents who present with both anxiety and depressive symptoms may require immediate suicidal assessment and therapeutic intervention.

ANXIETY AND DEPRESSIVE DISORDERS IN DSM-5

Of growing concern is the prevalence of subthreshold depressive and anxiety symptoms in the child and adolescent population. Those who do not meet full diagnostic criteria for either disorder may be overlooked and consequently not receive adequate treatment, more than quadrupling the risk for the development of an anxious or depressive psychiatric disorder.[70,71] The 12-month prevalence rates for subthreshold depressive disorders in children and adolescents range between 3% and 7%, and the lifetime prevalence rate through late adolescence has been reported to be as high as 26%.[70–72] A study conducted by Klein et al. reported that almost half of all adolescents with subthreshold depressive disorder in a community sample developed full syndromal depressive disorder by the time they were 30 years of age.[70] The study suggested that 7 unique variables, including anxiety syndrome, female sex, greater depression severity, increased medical conditions, history of suicidal ideation, psychomotor disturbance, and family history of depressive disorders significantly predicted the escalation from subsyndromal to full-syndrome depressive disorder in adolescents.[70] This finding substantiates the importance of documenting and treating subthreshold anxiety and depressive symptoms.

Earlier editions of the DSM have relied on categorical approaches to diagnosis (either patients meet criteria for a disorder or they do not). This diagnostic approach has limitations in the child and adolescent population, particularly because of the subsyndromal comorbid symptomatology described above. The DSM-5, however, has incorporated dimensional approaches to assessment and diagnosis. This dimensional assessment of psychopathology provides for a more accurate assessment of subclinical presentations of disorders, disorder severity, and how symptoms change dynamically over time (with repeated assessment).[73,74] Dimensional ratings can also be made to capture symptoms that cut across multiple

diagnoses, better representing the full presentation of symptoms within an individual and capturing diagnostic comorbidity.[73,74]

In addition to adopting a more dimensional approach, the DSM-5 Task Force carefully considered the order of diagnostic categories in the manual. Anxiety disorders follow depressive disorders, obsessive-compulsive and related disorders follow anxiety disorders, which are followed by trauma- and stressor-related disorders and then dissociative disorders. [75] This sequence is intended to emphasize the close relationships among some of the conditions in these adjacent sections.[75] Furthermore, the order of anxiety diagnoses in the anxiety section is intended to reflect the developmental progression of certain anxiety disorders. The typical age of onset is used to sequence the disorders, with separation anxiety disorder first in the chapter, followed by selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, and ending with generalized anxiety disorder.

Recognizing the prevalence and clinical implications of comorbid presentations (specifically subsyndromal anxiety symptoms in depression), the DSM-5 has included criteria for a specifier "with anxious distress" for major depressive disorder and bipolar disorder.[76,77] The anxious distress specifier is defined as the presence of at least 2 of the following anxiety symptoms during the majority of days of a depressive episode in major depressive disorder, or during an episode of mania, hypomania, or depression in bipolar disorder: feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful may happen, or feeling that one might lose control of oneself. In addition, a severity rating is to be applied to this specifier. Clinicians can rate the anxious distress as mild (2 of the above symptoms present), moderate (3 symptoms), moderate-severe (4 or 5 symptoms), or severe (4 or 5 symptoms with motor agitation). Adding a dimensional scale to these categorical diagnoses reflects the increasing awareness that the presence of anxiety symptoms can have a significant impact on the treatment course and outcomes of existing diagnoses.[77]

MOOD AND ANXIETY SYMPTOMS IN DIAGNOSTIC ASSESSMENTS BY CHILD AND ADOLESCENT SELF-REPORT

A concern in children and adolescents, particularly with younger children, is that their ability to express and verbally describe psychiatric symptoms—including anxiety and depressive symptoms—may be limited by language development and cognitive factors. Thus, psychiatric assessments commonly rely upon parents/caregivers, and other reliable informants such as teachers to provide information, as children are thought be unreliable reporters of their own mental state.[78] However, adult reporters may fail to accurately recognize mood symptoms in younger children; therefore, corroborating evidence concerning symptoms from the child's own perspective would be of value in a clinical diagnostic assessment.[78] Some studies have suggested that even young children may be able to report symptoms. Jensen and colleagues observed a correlation between child and parental reports of various psychiatric diagnoses in children and adolescents aged 9 to 17 years,[79] and they specifically noted that reports about internalizing symptoms (eg, depression, anxiety) are highly correlated between child and parent informants.[79] This

finding suggests that children may be reliable reporters of their symptoms, particularly internalizing symptoms, and that they can add valuable information to the psychiatric diagnostic process.[78,79] In addition, Luby et al. evaluated the validity of symptom reporting by preschool age children (4 to 5.6 years of age)[78] and found a strong relationship between younger children's self-reports of basic depressive and anxious symptoms and their parents' reports of these symptoms,[78] although some difficulty was observed with regard to the reporting of abstract psychiatric symptoms (eg, loneliness, self-esteem). Taken together, these findings suggest that parents are able to accurately assess and report their child's symptoms and, conversely, that children, even at young ages, are able to provide accurate information to help inform the diagnostic assessment.[78,79]

PSYCHOPHARMACOLOGIC TREATMENT OF ANXIOUS-DEPRESSION IN YOUTH

In contrast to the many psychopharmacologic treatment studies that have evaluated adult patients with "anxious depression,"[80–83] pediatric studies have largely focused on patients with depression or anxiety (eg, social phobia, separation anxiety disorder, GAD, or the combination) and have generally excluded anxious patients with comorbid MDD.[84–88] Abundant evidence suggests that selective serotonin reuptake inhibitors (SSRIs) are effective in treating both pediatric MDD and anxiety disorders,[89–91] and, on the basis of randomized controlled trials of SSRIs and selective serotonin norepinephrine reuptake inhibitors (SNRIs) (Table 1), recommendations can be extrapolated regarding the treatment of anxious depression in pediatric patients.

Like psychopharmacologic treatment studies in pediatric patients with MDD, most clinical trials in pediatric patients with anxiety disorders have focused on SSRIs and SNRIs. In general, studies of pediatric anxiety disorders have focused on anxiety as a homogeneous entity (eg, "childhood anxiety" or the combination of separation anxiety disorder, GAD, and social phobia/social anxiety disorder).[88,91] More recently, however, several studies have focused on specific anxiety disorders (eg, GAD, separation anxiety disorder) in these populations.[86,87,92] In randomized, controlled trials of patients with multiple anxiety disorders, fluvoxamine has been associated with significant clinical improvement and is generally well-tolerated; however, these trials excluded patients with MDD.[95] Two open-label trials of fluoxetine in pediatric patients with mixed anxiety disorders have also suggested benefit in alleviating anxiety symptoms.[92] In addition, in a randomized placebo-controlled trial of pediatric patients with GAD, separation anxiety disorder, and social anxiety disorder, improvement was observed on all efficacy measures in patients treated with fluoxetine.[93]

Fixed-dose treatment studies of sertraline in children aged 7–17 years of age found improvement as demonstrated by decreased severity of anxiety symptoms.[85] In addition, the Child/Adolescent Anxiety Multimodal Study (CAMS) that involved 488 patients found that the effect of sertraline monotherapy was superior to that of placebo and similar to that of cognitive behavioral therapy (CBT), while combination treatment was superior to both monotherapy conditions.[88] In both of these pediatric trials, sertraline was well-tolerated.

Fluoxetine and venlafaxine have also been evaluated in pediatric patients with GAD and both were found to be superior to placebo.[86,93] However, some issues related to the tolerability of venlafaxine in the pediatric population were noted, as venlafaxine was associated with increased blood pressure, asthenia, pain, anorexia, somnolence, and weight loss and it may also have been associated with treatment-emergent suicidal ideation.[86] Finally, one randomized, placebo-controlled trial that examined the efficacy and tolerability of flexibly-dosed buspirone (15–60 mg daily) in children and adolescents with GAD (ages 6 to 17 years) found no difference between buspirone and placebo.[111]

Paroxetine, citalopram, fluoxetine, and venlafaxine have been evaluated in pediatric patients with social phobia. In a randomized trial, patients treated with paroxetine had response rates of 78% versus 38% for placebo over the course of 16 weeks.[94] However, adverse events, including withdrawal symptoms, were twice as likely with paroxetine treatment. Venlafaxine extended release (ER) was associated with improvement in pediatric social anxiety disorder. [84] One placebo-controlled trial of pediatric patients with social phobia (7–17 years of age) compared Social Effectiveness Therapy for Children (SET-C) and fluoxetine.[92] SET-C included psychoeducational modules, social skills practice in group sessions, social exposures, and individual psychotherapy. Both fluoxetine and SET-C were superior to placebo. Fluoxetine appeared have maximum effect at 8 weeks. Fluoxetine was well tolerated with no reported severe adverse events.[92] Finally, open-label studies of citalopram (10–40 mg/d)[112] and escitalopram (10–20 mg/d)[113] in pediatric patients with social anxiety disorder demonstrated benefit and tolerability.

To date, we are aware of no treatment studies or recommendations that address the management of coexisting anxiety and depression (whether comorbid or subsyndromal) in the pediatric population. However, extrapolation from the available evidence for the psychotherapeutic and psychopharmacologic treatment of both MDD and anxiety disorders in youth suggests that multimodal approaches are superior to monotherapy[88,92,96,114] Thus, both the Treatment of Adolescent Depression Study (TADS)[115] and the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)[114] study suggest that the combination of an SSRI (or SNRI in the case of TORDIA) plus CBT is superior to monotherapy. Similarly, in children and adolescents with anxiety disorders, treatment with the combination of CBT and sertraline was found to be superior to monotherapy.[88] Thus, a first-line approach to the pediatric patient with coexisting anxiety and depression should include evidenced-based psychotherapy in conjunction with an SSRI (Figure 1), given that several SSRIs (eg, sertraline, fluoxetine) have strong evidence of efficacy in both disorders. Alternatively, monotherapy remains an available option for a first-line intervention in pediatric patients with anxiety and depression as SSRIs and several evidence-based psychotherapies are also supported by available evidence as monotherapy for these conditions. With regard to the specific modality of psychotherapy, there is strong evidence for several types of psychotherapy in the available literature on pediatric anxiety and depression, including CBT, [100,114] interpersonal psychotherapy for adolescents (IPT-A),[116] and psychodynamic psychotherapy[117,118]

Despite the potential efficacy of these "first-line" interventions in youth, many young patients with depressive or anxiety disorders continue to experience residual symptoms.[119] It

has also been suggested that pediatric patients with comorbid anxiety and depression may have a lower likelihood of achieving remission.[119] Currently available data suggest that patients with depressive symptoms (in major depressive disorder) and residual anxiety symptoms (in generalized, social, or separation anxiety disorders) may show benefits after switching from their initial SSRI regimen to an alternate SSRI regimen.[114,120] However, beyond switching from one SSRI to another SSRI, data regarding "next step" interventions are limited. Thus, at this level of the treatment algorithm for comorbid anxiety and depression in pediatric patients (Figure 1) our recommendations represent the "expert opinion" level of evidence and are primarily based on data extrapolated from adult studies. Thus, on the basis of double-blind, placebo-controlled trials evaluating the use of quetiapine as an adjunct to ongoing treatment with an antidepressant medication in SSRI-resistant MDD,[121,122] and an open-label trial of quetiapine as an adjunct to antidepressant medication in the treatment of SSRI-resistant depression in children and adolescents[123] as well as positive double-blind, randomized controlled trials of quetiapine monotherapy in adults with GAD,[124,125], it is reasonable to consider quetiapine as an adjunctive agent in the treatment of SSRI-resistant and psychotherapy-resistant depressive or anxiety symptoms in children and adolescents. However, the risks and benefits of second-generation antipsychotic medications should be carefully considered, in accordance with guidelines from the American Academy of Child and Adolescent Psychiatry.[126] In addition, based on positive double-blind, placebo-controlled studies evaluating the use of aripiprazole as an adjunct to ongoing treatment with an antidepressant medication in adults with treatment-resistant MDD[127,128] and a positive, open-label trial of aripiprazole as an adjunct to SSRI treatment for SSRI-resistant generalized anxiety disorder in adults,[129] as well as a retrospective evaluation of aripiprazole as an adjunct to SSRI treatment in depressed and anxious adults, [130] it is possible that adjunctive aripiprazole may have a role in the management of functionally impairing depressive or anxiety symptoms that persist in youth with anxious depression, following initial trials of SSRIs and psychotherapy. It is interesting that post-hoc analyses of trials with both aripiprazole and quetiapine have suggested that these agents may have efficacy for anxious depression.[83,131] However, use of second-generation antipsychotic medications has been associated with significant adverse effects, including weight gain, diabetes or insulin insensitivity, dyslipidemia, and potential tardive dyskinesia. Thus, the risk and benefits of any medication changes should be weighed to ensure optimal therapeutic outcomes.

CONCLUSION AND IMPLICATIONS FOR FUTURE RESEARCH

Child and adolescent populations most often present with anxiety and mood symptoms that co-occur, which leads to a more difficult diagnostic assessment, increased symptom severity, and complicated treatment methods.[1–6,21] In addition, a number of specific considerations arise in treating child and adolescent populations that are not always primary factors in adults, including unique presentations of symptoms (eg, increased somatization, irritability, and agitation), functional impairment in school and social activities during developmentally important years, significantly increased risk for suicidality, and influences from the family system. Although research concerning overlapping anxiety and depressive symptoms in this

population is available, more work is warranted to gain a better understanding of the unique factors involved in child and adolescent presentations.

Our review of the available literature suggests that education regarding the anxiety/mood symptoms that present in youth be disseminated to parents, teachers, counselors, school administrators, coaches, physicians, and other caretakers and providers. Furthermore, school refusal and somatic complaints should be considered important indicators that a child/adolescent may be experiencing significant distress due to anxiety and/or depression.[31] The implementation of school-based screening and counseling programs geared to the needs of anxious/depressed children and adolescents may enhance early detection, prevention, and appropriate referrals for those with more severe/chronic illness.[33] The lack of available data concerning the validity/reliability of assessments of comorbid anxiety and depression in youth is of concern, especially considering that earlier research suggests that youth are prone to significant impairment from co-occurring subsyndromal anxiety/depressive symptoms. Future research should also further explore the utility of available pharmacological and psychosocial treatments in the treatment of comorbid anxiety and depressive disorders in this population.

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Clarify diagnosis ⟶

Diagnosis confirmed for both anxiety disorder and MDD?

Treat primary disorder with psychotherapy or SSRI as clinically appropriate ⟵ No   Yes

Clarify manner in which the two disorders occur relative to one another

SSRI

Consider fluoxetine or sertraline as first line interventions given evidence in both pediatric anxiety disorders and pediatric MDD

and

or

Psychotherapy

Consider CBT or IPT-A or psychodynamic as first line interventions given evidence in both pediatric anxiety disorders and pediatric MDD

Residual depressive or anxiety symptoms?

Continue

Re-evaluate treatment in 6-12 months.

⟵ No   Yes

Add/Switch

Add SSRI if not begun, or change to another SSRI or venlafaxine

Residual depressive or anxiety symptoms?

No   Yes

Augmentation

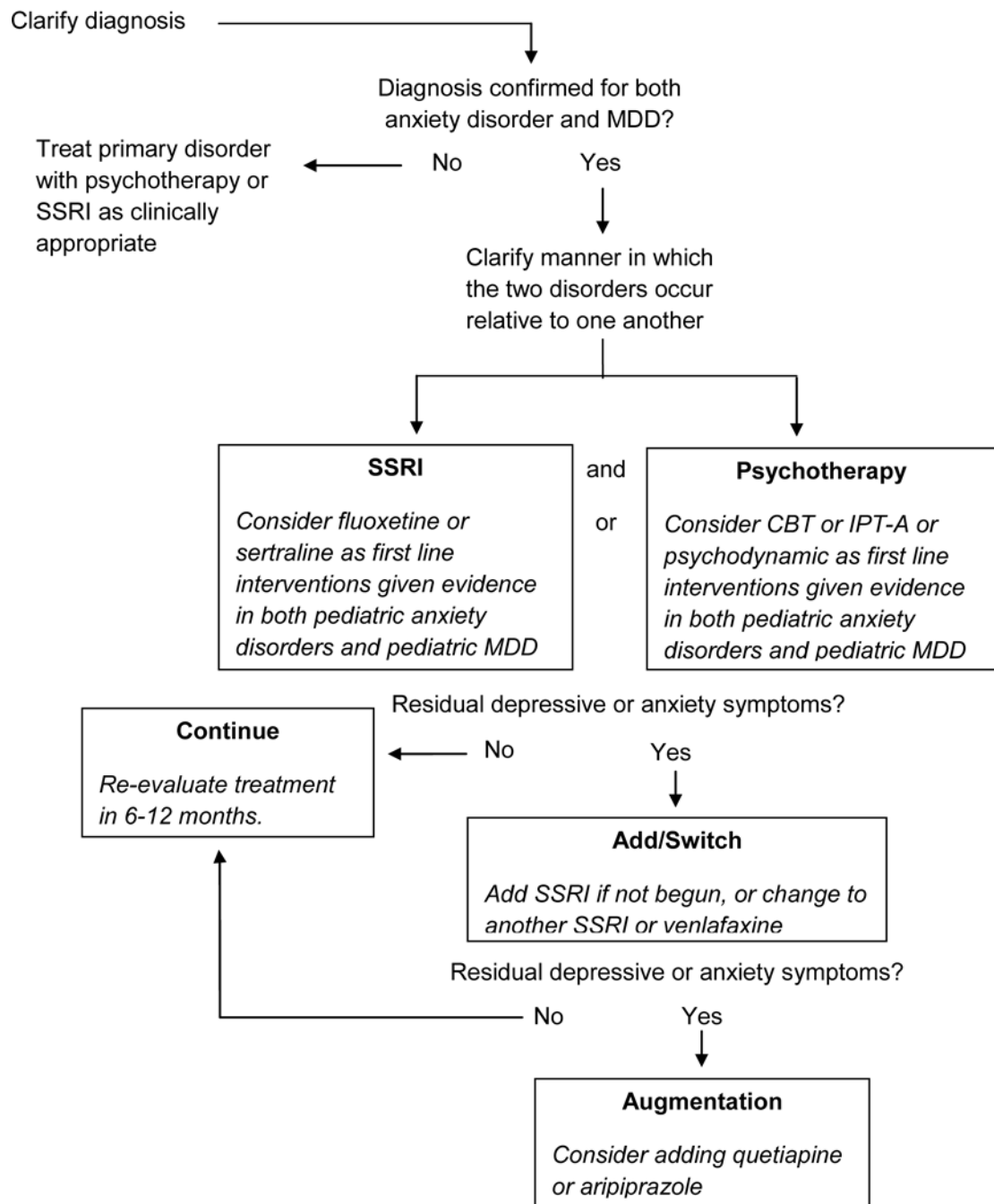*Consider adding quetiapine or aripiprazole*

Figure 1: Proposed algorithm for the treatment of comorbid anxiety and depression in children and adolescents.

Note: MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; CBT, cognitive-behavioral therapy; IPT-A, interpersonal psychotherapy for adolescents

Table 1:

Randomized Controlled Trials of Selective Serotonin Reuptake Inhibitors (SRIs) and Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) in Pediatric Anxiety Disorders

Medication		Anxiety Reference	Anxiety Disorder	Anxiety Dose Range (mg/day)	Anxiety Effect Size	MDD Reference	MDD Dose Range (mg/day)	MDD Effect Size
		PEDIATRIC ANXIETY DISORDERS				**PEDIATRIC MAJOR DEPRESSIVE DISORDER**		
SSRIs	Sertraline	Walkup et al 2008[88]	GAD SoP SAD	25–200	0.4	Wagner et al 2003[96]	50–200	0.28
		Rynn et al 2001[85]	GAD	25 (week 1) 50 (week 2–9)	0.7			
	Fluoxetine	Beidel et al 2007[92]	SoP	10–40		Simeon et al 1990[97]	20	0.21
		Birmaher et al 2003[93]	GAD SoP SAD	10 (week 1) 20 (week 2–12)	0.2	Emslie et al 1997[98]	20	0.60
						Emslie et al 2002[99]	20	0.50
						March et al 2004[100]	10–40	0.40
	Paroxetine	Wagner et al 2004[94]	SoP	10–50		Keller et al 2001[101]	20–40	0.22
						Berard et al 2006[102]	20–40	0.07
						Emslie et al 2006[103]	10–50	−0.06
	Fluvoxamine	RUPP 2001[95]	GAD SoP SAD	300 (maximum)	0.5	N/A not studied		
	Citalopram					Wagner et al 2004[104]	20–40	0.32
						von Knorring et al 2006[105]	10–40	−0.01
	Escitalopram	Ongoing trials				Wagner et al 2006[106]	10–20	0.13
						Emslie et al 2009[107]	10–20	0.27
SSNRIs	Venlafaxine ER	March et al 2007[84] Rynn et al 2007[86]	SoP GAD	37.5–225 37.5–225	0.9 0.4/0.5	Emslie et al 2007[108]	37.5–200	0.14
	Duloxetine	Strawn et al 2015[87]	GAD	30–120	0.48	Emslie et al 2014[109]	30–120	N/A, neg.
						Atkinson et al 2014[110]	30–120	N/A, neg.