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Sequential Comorbidity of Anxiety and Depression in Youth: Present Knowledge and Future Directions

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Abstract: Research suggests that a history of childhood anxiety correlates with and predicts adolescent depression. The present review synthesizes current knowledge of relations between childhood anxiety and adolescent depression, focusing on the possibility that primary anxiety in childhood may cause secondary depression in adolescents. Across existing studies, evidence strongly supports childhood anxiety as a risk factor for adolescent depression, and long-term follow-up studies of cognitive-behavioral childhood anxiety treatments may suggest a causal anxiety-depression link. However, mechanisms underlying this relationship remain unexplored. Future directions include careful assessment of comorbidity between anxiety and depressive disorders, longitudinal evaluations of anxiety and depression following interventions for childhood anxiety, and investigations of mediators and moderators of the anxiety-depression link. Finally, mechanisms by which the treatment of childhood anxiety might prevent depression in adolescents are proposed.

Keywords: Adolescents, anxiety, children, comorbidity, depression, prevention, sequential comorbidity.

INTRODUCTION

Anxiety and depression in youth are highly damaging and prevalent [1]. Individually, both kinds of disorders impair interpersonal relationships, emotional well-being, and academic achievement; when occurring comorbidly, they more strongly predict suicide attempts, increased utilization of mental health services, and functional impairment than either disorder alone [2-4]. In the past two decades, research has suggested that a history of anxiety disorders in childhood may predict or cause adolescent depression [4-8]. The present review aims to examine the possibly causal pathway between childhood anxiety and adolescent depression, updating and extending understandings of the anxiety-depression link. We assess relations between childhood anxiety and adolescent depression, outline mechanisms by which primary anxiety might precipitate secondary depression in youth, and address implications for the treatment and prevention of anxiety and depression. Given a possible causal link between early anxiety and later depression, a secondary benefit of interventions targeting childhood anxiety may be a reduction in subsequent depression.

ANXIETY AND DEPRESSION: EPIDEMIOLOGY & COMORBIDITY

Anxiety: Prevalence, Onset, and Course

Point prevalence rates of anxiety disorders from mixed-gender, community youth samples have ranged from 2.6-4.1% [9-10]. The wide range of estimates across studies likely results from different kinds of anxiety disorders being measured, which typically include some subset of social anxiety disorder (SAD), generalized anxiety disorder (GAD), specific phobia (SP), panic disorder (PD), separation anxiety, and obsessive-compulsive disorder (OCD). Epidemiological studies of specific anxiety disorders in youth inconsistently report rates by age or gender. However, overall rates suggest that separation anxiety affects approximately 3-5% of children but only 0.01-2.4% of adolescents at any given time [11]. Point prevalence rates of PD are estimated at 1-2% of adolescents and slightly lower in children [12]. SAD and GAD have been reported as affecting 7% and 4.3% of youth at any given time, respectively, while point prevalence rates of OCD have been identified as 1% in children and up to 4% in adolescents [13-14].

Overall, anxiety disorders tend to emerge during middle childhood and adolescence, with some subtypes (e.g., SP, separation anxiety) manifesting earlier than others (e.g., SAD) [1]. The typical course of anxiety disorders across youth has been described as chronic and persistent [12]. Anxiety symptomatology tends to fluctuate across threshold and subthreshold levels, with frequent diagnostic shifts within the anxiety spectrum (e.g., shifts from separation anxiety or SP as a younger child to SAD or GAD in mid- or late-childhood) [12].

Depression: Prevalence, Onset, and Course

Rates of major depression increase drastically from childhood to adolescence, with yearly incidence rates rising from 2-3% for 6-11 year olds and from 3-8% for 11-15 year olds [14-15]. By the time they are age 18, as many as 20% of

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adolescents will have experienced an episode of major depression [6].

The median age of onset for depression occurs in mid- to late-adolescence [16], and the prevailing pattern in the course of major depression is episodic rather than chronic. On average, depressive episodes last six months. One third of people who develop depression have chronic depression in the first three decades of life. Of the remaining two-thirds, half report complete remission, and half report recurrent episodes with full remission in between [17].

Anxiety and Depression: Comorbidity in Youth

In addition to being the most frequent psychiatric diagnoses among youth, anxiety and depression co-occur at alarmingly high rates, with point prevalence rates of comorbidity ranging from 20-50% in clinical samples [18]. Interestingly, co-occurrence of anxiety and depression does not appear to be symmetrical. There tend to be more cases in which youth with primary depressive disorders have comorbid anxiety than cases in which youth with primary anxiety disorders have comorbid depression [19-21]. While anxiety is more prevalent during childhood, depression increases during adolescence [22-23]. Youth with comorbid anxiety and depression tend to be older than those with either disorder alone [20].

LINKS BETWEEN CHILDHOOD ANXIETY AND ADOLESCENT DEPRESSION

Longitudinal, community-based research suggests that children experiencing any anxiety disorder are 2.2 times more likely to experience a depressive episode in adolescence [24]. Given the high proportion of children with anxiety who later develop depression, might early anxiety predict or cause subsequent depression? Before exploring this possibility, it is crucial to define common terms in risk factor research. Due to inconsistencies across the field, Kraemer and colleagues have suggested that the terms "correlate," "risk factor," and "causal risk factor" be standardized across research [25]. Their work defines "correlate" as a variable that is associated with the outcome, but not necessarily predictive of that outcome. In contrast, a "risk factor" can be shown to predict a given outcome. Finally, a "causal risk factor" is a risk factor that can be manipulated to change the likelihood of the outcome it predicts. The present discussion will employ these definitions in describing links between primary anxiety and secondary depression in youth.

Childhood Anxiety as a Correlate of Adolescent Depression

Research has continually found correlations between childhood anxiety and subsequent depression. For instance, young adults (mean age: 22) with histories of childhood anxiety have reported depression at significantly higher rates than young adults with no history of childhood anxiety [26]. Another study suggested that children described by parents as fearful and reticent at age 3 showed more depressive symptoms by age 21 [27]. Further, Brady and Kendall found that, across epidemiological studies, 15.9% to 61.9% of children identified as anxious or depressed had comorbid anxiety and depressive disorders at the time of assessment, that scores on anxiety and depression were highly correlated, and that anxiety symptoms tended to predate depressive symptoms [28]. Additionally, a retrospective study found strong correlations between depression in young adulthood and diagnoses of GAD in childhood [29]. Overall, this research documents that anxiety and depression are correlates, though it cannot discern the direction of the disorders' relationship across youth.

Childhood Anxiety as a Risk Factor for Adolescent Depression

A number of longitudinal, prospective studies indicate that anxiety is a risk factor for subsequent depression [16, 29-30]. Although much of this work has explored young adult samples, some has assessed predictive patterns among youth. Cole and colleagues examined the temporal relation between anxiety and depressive symptoms in children (n = 330) over a three-year period [31]. Across self and parent reports, high levels of anxiety symptoms at a single point in time predicted higher levels of depressive symptoms at subsequent points in time, even after controlling for prior depressive symptoms. Further, a retrospective longitudinal study of adolescents (n=3,021; ages 14-24) suggested that the presence of any anxiety disorder at baseline predicted increased risk for subsequent depression, with GAD, panic disorder, and SAD most substantially increasing risk [32-33]. Another longitudinal study of young adults for whom prior psychiatric records were available (n=996; ages 18-21 at time of study) found that early anxiety increased risk for depressive disorders across adolescence and young adulthood. These results suggested a dose-response model of risk, in which children reporting higher, more severe anxiety symptoms at age 8 were at greatest risk for developing depression later in life [33]. Taken together, these findings largely support the supposition that anxiety in childhood precedes and predicts increased risk for depression across development. However, they do not demonstrate that anxiety *causes* secondary depression in youth.

Childhood Anxiety as a Causal Risk Factor for Adolescent Depression

While research has supported the hypothesis that anxiety increases risk for depression, a causal relationship between the disorders is far more challenging to demonstrate. Ultimately, if such a link exists, then reduction or alleviation of anxiety disorders should result in decreases (or lack of increases) in subsequent depression. Preliminary support for this hypothesis comes from longitudinal studies that examine reductions in depression as a secondary outcome of cognitive-behavioral therapy (CBT) programs for youth anxiety [7, 34-36]. For instance, Saavedra and colleagues examined the long-term effects of CBT for youth who had participated in earlier randomized trials of anxiety disorders [37a, 37b]. They reported the extent to which participants displayed other anxiety disorders and depression 8 to 13 years post-treatment. The researchers found evidence for the long-term efficacy of CBT for childhood anxiety disorders

and secondary psychiatric problems in young adults. Not only were improvements in anxiety maintained from post-treatment, but participants' depression levels were significantly lower than rates found in longitudinal studies of non-treated anxious youth. Separately, Kendall and colleagues assessed effects of CBT for youth anxiety 7.4 years post-treatment [7]. Initial treatments gains maintained for anxiety disorders and rates of depression in intervention participants were no different than general population rates. The authors suggest that, given high rates of sequential comorbidity of anxiety and depression in youth, one might expect to find much higher rates of depression in an anxious sample compared with the general population. Thus, depression might have been ameliorated by the treatment for anxiety received 7.4 years earlier. Together, these studies suggest that treating anxiety in children (a) help ameliorate both anxiety and depression over time, or (b) might positively affect the sequelae of secondary depressive disorders across adolescence and young adulthood. However, anxiety symptoms and disorders were assessed variably across these studies [7; 37a, 37b]. Some employed aggregate anxiety scores for outcome analyses, while others selected participants with GAD or SAD diagnoses. Further, intervention effects on depression were not assessed through the randomized controlled trials, limiting conclusions about direct intervention effects on depression. Finally, temporal order of intervention effects on anxiety and depression was not directly explored in these studies, limiting or anxiety's potential effect on depression over time. Due to these variations, it remains unclear whether amelioration of certain anxiety disorders or symptoms in childhood might show particular links to reduced secondary depression in adolescence.

POTENTIAL PATHWAYS FOR THE ANXIETY-DEPRESSION LINK

While research suggests a strong link between primary anxiety and secondary depression in youth, knowledge of the mechanisms underlying this link remains inconclusive. Further, the sequentially comorbid relationship between anxiety and depression likely involves a wide variety of cognitive, social, environmental, and biological factors. Investigators have thus proposed a variety of pathways that might explain the anxiety-depression link. Garber and Weersing [20] note that these pathways have generally followed three structures (see Fig. **1**). The first suggests that anxiety and depression might represent a single disorder, with differences between anxiety and depression symptoms reflecting different developmental phases. The second proposes that common risk factors lead to both anxiety and depressive disorders, triggering anxiety earlier in life. Third, anxiety symptoms themselves may increase maladaptive thoughts and behaviors in children that contribute to the development of depression: that is, mediating variables might explain the disorders' sequential comorbidity. However, it is unlikely that any one of these pathways can fully explain the relationship between primary anxiety and secondary depression. Rather, as suggested by Epkins and Heckler's cumulative interpersonal risk model of anxiety and depression [38], shared antecedents, risk factors, and moderating and mediating variables may compound to precipitate both anxiety in children and depression in adolescents. To address this possibility, the present section has two aims. First, it describes the three kinds of previously suggested pathways for the anxiety-depression link. Second, it suggests previously unexplored mechanisms by which anxiety might lead to depression in youth.

Pathway #1: Two Manifestations of One Diagnosis

Some investigators have questioned whether there is a valid and useful distinction between anxiety and depression in youth [39]. Specifically, the overlap in the measurement of anxiety and depression has led to controversy regarding the nature of the relationship between the disorders. Early studies of depression among children typically compared groups of depressed children to groups of nondepressed peers, often using the Children's Depression Inventory (CDI) [40]. Likewise, studies of anxiety among youth compared anxious children with nonanxious peers and typically used the Revised Children's Manifest Anxiety Scale (RCMAS) [41] to measure differences. However, in studies comparing scores on both the CDI and the RCMAS, children often displayed symptoms of both disorders, with correlations between depression and anxiety ranging from 0.5-0.7 [42, 43]. Some researchers have viewed this overlap as a product of poor discriminant validity between youth measures for depression and anxiety [26]. Indeed, Seligman and Ollendick [8] have suggested that measures such as the CDI and the RCMAS may be insufficient to differentiate anxiety from depression in youth. However, other investigators have hypothesized that the two kinds of disorders cannot or should not be distinguished in childhood, as they are simply variations of the same syndrome [44, 45].

A few studies have found support for a unified anxiety-depression model among young children and early adolescents. For instance, research by Cole and colleagues [5] found substantial correlations between anxiety and depression symptoms among third-grade children (r=.90), even after controlling for shared method variance. Sixth graders demonstrated a somewhat smaller, though still strong correlation (r = .72) between the anxiety and depression symptoms. The researchers proposed that if anxiety and depressive diagnoses are, in fact, indistinguishable in young children, then the term "negative affectivity" might more adequately describe their diagnoses than "anxiety" or "depression." They also suggested that anxiety and depressive disorders might become more distinct with age: thus, perhaps Clark and Watson's [46] tripartite model of anxiety, depression, and negative affectivity might apply to older children, adolescents, and adults, but not to young children. This theory delineates that, by late childhood, anxiety and depression are distinct, but negative affectivity is present in both kinds of disorders.

Some research has supported the differentiation of anxiety and depression in youth [8, 47, 48]. These investigations have supported the utility of a two-factor theory of anxiety and depressive disorders in children as young as eight years old. While controversy over the disorders' status has yet to be resolved, the debate reflects issues of measurement and validity in internalizing disorders in children. This conversation may inform (1) the creation of more valid and precise assessments of childhood symptoms of depression

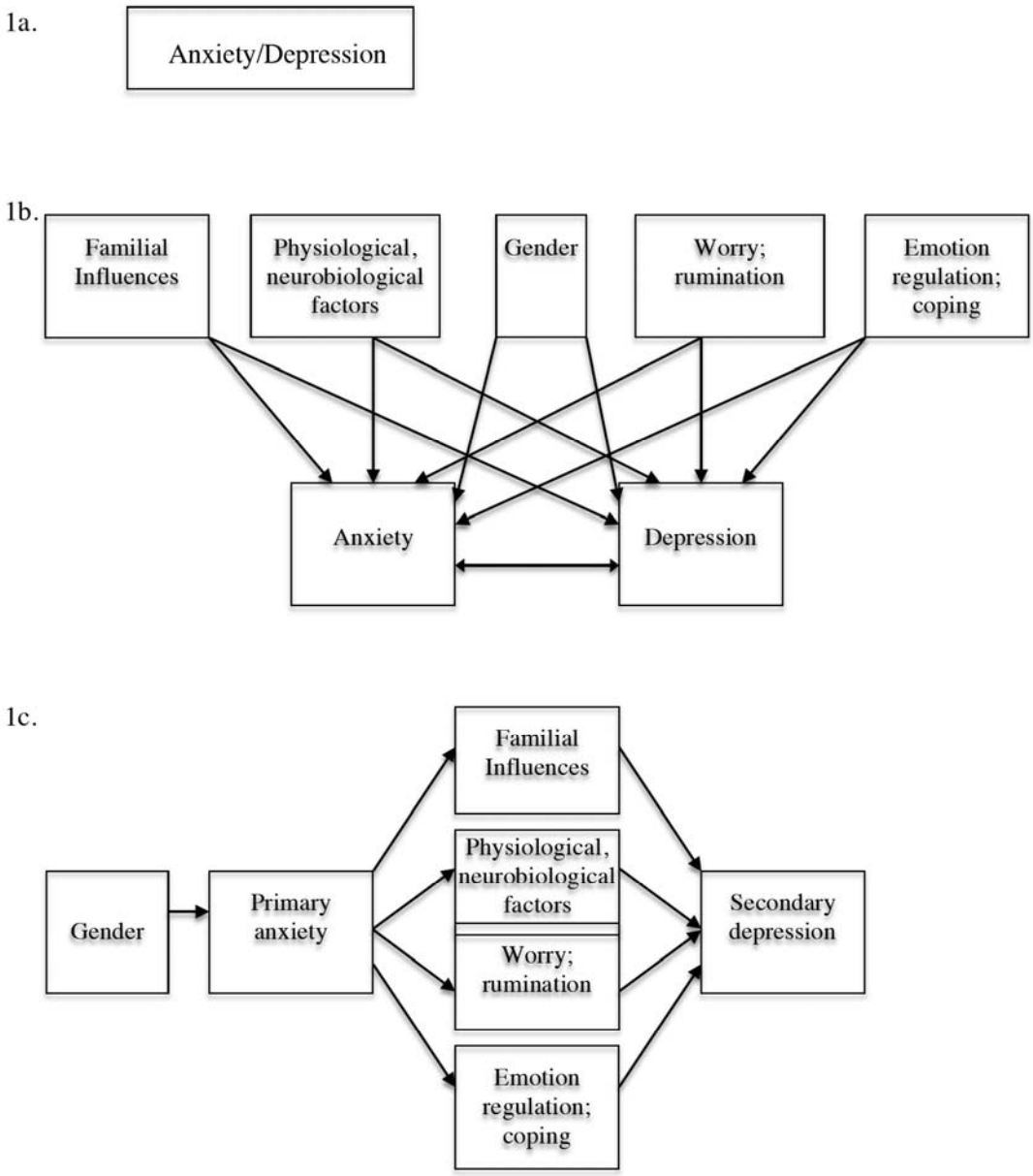

Fig. (1). Three distinct pathways by which primary anxiety might lead to secondary depression in youth. **a**. Anxiety and depression are developmentally appropriate manifestations of the same disorder. **b**. Shared risk factors lead to both primary anxiety and secondary depression. **c**. Primary anxiety exacerbates risk factors, which, in turn, increase likelihood of development depression.

and anxiety, and (2) sound research designs regarding depressive, anxious, or negative affectivity in youth.

Pathway #2: Common Risk Factors Lead to Primary Anxiety and Secondary Depression

Familial Influences

Longitudinal, cross-sectional, and observational family studies have continually found that children with depressed parents are at higher risk for developing anxiety and depression across development [49, 50]. This intergenerational transmission of internalizing disorders might reflect both genetic markers and environmental influences that precipitate anxiety and depression in youth [20].

Twin studies have demonstrated that common genetic influences might partially explain the high heritability of anxiety and depression [51, 52]. Proposed phenotypic overlaps linked to genetic predispositions to anxiety and depression may include negative affectivity, hyperarousal, pessimistic attributional style, and several cognitive biases including interpretation of threat [20, 53]. Further, consistent with longitudinal studies showing sequential comorbidity, a shared genetic predisposition may be expressed as anxiety earlier in childhood and depression in adolescence or adulthood [54]. Researchers have theorized that the progression from anxiety to depression in youth reflects changing developmental capacities to exhibit and experience certain symptoms. For instance, younger children might more easily

express stress through somatic pains or agitation (physiological symptoms of anxiety), while older children are cognitively equipped to experience rumination (a cognitive symptom of depression).

Although still in its early stages, new research suggests that epigenetic processes may confer additional risk for internalizing problems in youth. Epigenetics involves changes in gene expression or cellular phenotype, often mediated through interactions with the environment rather than changes in underlying DNA sequences, that affect the expression or "silencing" of genetic predispositions [54]. For example, Weaver and colleagues [55] demonstrated intergenerational transmission of behavioral change through epigenetic processes with their experimental and cross-fostering studies of rats. The quality of maternal care (measure by licking and grooming behavior), which is associated with the offspring's stress response, can be altered over multiple generations in the glucocorticoid receptor gene, influencing the next generation's stress regulation. Given the relevance of stress regulation to depressive and anxiety disorders, future research may explore how epigenetic processes may confer risk for youth, given environmental stressors.

Genetic predispositions, and potentially, epigenetic processes, only partially explain intergenerational transmission of anxiety and depression, however. Parenting styles also appear to play a role in the development of internalizing disorders. For instance, parental rejection and hostility are strongly linked to depression in children, while parental control is strongly linked to childhood anxiety [56]. Other research has corroborated the finding that both parental rejection and control correlate positively with childhood anxiety and depression, with rejection showing stronger associations with depression, and control, with anxiety [57].

Physiological and Neurobiological Factors

Research on the psychophysiology of anxiety and depression has largely focused on the hypothylamical-pituitary-adrenal (HPA) axis, which helps to regulate the body's stress response [58, 59]. Healthy adjustment relies on the ability of the HPA to produce normative increases in cortisol under stress and reduce production when stress is removed. However, chronic exposure to stress or genetic predispositions may predispose youth to anxiety and depressive disorders by causing chronic overproduction of cortisol, along with other hormones, in the HPA system. Indeed, children and adolescents with anxiety and depression symptoms tend to have higher baseline levels of cortisol compared to aged-matched healthy controls [59].

Other studies have indicated the presence of shared neurobiological patterns in anxiety and depression. Stressful experiences have been shown to produce specific changes in brain structure and function, especially in limbic regions such as the amygdala [60]. The amygdala has been implicated in processing and responding to emotional information [61] and plays an important role in navigating the emotional safety of one's environment. Neuroimaging studies show that previously stressed adults have exaggerated amygdala responses to threatening stimuli, relative to nonstressed controls [62, 63]. Further, several studies suggest that amygdala structure and function may mediate relations between environmental stress and subsequent anxiety and mood disorders. Amygdala volumes are larger and the amygdala is more reactive in youth with anxiety and depression compared to healthy controls [64-66]. One study found that children who experienced orphanage care, compared to a comparison group, had larger amygdala volumes, poorer emotion regulation, and increased internalizing problems [67]. Further, the presence of internalizing problems at baseline did not drive group differences in amygdala volume, suggesting that amygdala structure and function might confer risk for the development of these problems in youth subjected to early adversity.

Rumination and Worry

A third shared risk factor for anxiety and depression might be experiencing repetitive, uncontrollable thoughts: specifically, rumination, worry, or both. Nolen-Hoeksema [68] defines depressive rumination as repetitive thoughts concerning the causes and consequences of depressive symptoms. For instance, rumination may involve repetitive, intrusive thinking about how a negative life event affects one's present mood. Separately, worry has been conceptualized as excessive thought involving the consequences of a negative event that might occur in the future [69].

In numerous cross-sectional studies, rumination has shown associations with depressive disorders and depressive symptoms in children, adolescents and adults [e.g., 70-74]. Further, longitudinal studies have found that rumination predicts increases in depressive symptoms among third grade children and early adolescents, over time periods ranging from six weeks to seven months [75-79]. Separately, research has assessed the link between worry and anxiety. Borkovec and colleagues [69] found strong associations between worry, muscle tension, difficulty refocusing thoughts, and anxiety symptoms. While few longitudinal, prospective studies have explored the direction of the relationship between worry and anxiety, one study found that worry predicted anxious arousal, whereas anxiety did not predict worry [80].

The majority of research has examined worry in relation to anxiety and rumination in relation to depression. However, a few studies have investigated potential links between worry and depression and between rumination and anxiety. For instance, Andrews and Borkovec found that experimentally induced worry contributed to both anxious and depressed moods in adults [81], and Nolen-Hoeksema found rumination in adults prospectively predicted both depression and anxiety symptoms, controlling for initial levels of symptoms [82]. Further, studies have found that rumination predicts symptoms of anxiety [83, 84], social phobia [85], posttraumatic stress disorder [86], and GAD [87]. These findings suggest that rumination and worry may each contribute to the development of both depressive and anxiety disorders.

Calmes and Roberts [88] explored this possibility, assessing worry and rumination as prospective predictors of anxiety and depression in adults over a 6-8 week period. This study found that rumination and worry predicted symptoms of anxiety but not of depression. These findings suggest a

more immediate impact of repetitive thought on symptoms of anxiety. Later effects on subsequent depression—that might emerge after the 6-8 week period examined by Calmes and Roberts—were unexamined in this study. Given prior research on the contributions of negative, repetitive thought to the development of depression [68], it seems possible that worry and rumination may predict not just anxiety in the short-term, but both anxiety and depression in the longer term, as well. Indeed, a prospective, longitudinal study found that rumination predicted both anxiety and depression in a community sample of early adolescents across a seven-month period [77]. Thus, uncontrollable, repetitious thoughts appear to be a latent risk factor for both anxiety and later depression. Research should continue to assess longitudinal relationships between worry, rumination, anxiety, and depression, as well as whether these findings apply to children younger than early adolescents.

Emotion Regulation and Coping

Difficulties with emotion regulation and coping might also increase risk for both childhood anxiety and adolescent depression. Emotion regulation is the ability to modify one's emotional states, thoughts, experiences, or expressions in an adaptive manner given environmental demands [89]. Investigators have suggested that poor emotion competence is a core component of internalizing psychopathology [90, 91]. However, coping and emotion regulation are highly heterogeneous concepts, involving a number of distinct skills and subject to diverse conceptualizations [89]. Thus, in order to delineate the relevance of emotion regulation and coping strategies to anxiety and depression, research must first identify particular deficits common to both kinds of disorders.

One emotion regulation strategy that appears characteristic of both anxiety and depression in youth is avoidance coping: withdrawing from, or trying not to think about, situations viewed as potentially unpleasant or threatening. While this strategy is used normatively by children and adolescents in everyday life, anxious and depressed youths often over-rely on avoidance coping [92], perhaps because they tend to overestimate the intensity and duration of negative emotions that events viewed as harmful might cause [93-94]. As suggested by Trosper and colleagues, youths with internalizing problems might fail to realize that chronic avoidance may prevent the natural reduction of fear and upset that result from habituation to possibly negative experiences [92]. Avoidance may also prevent youth from developing skills that would allow them to navigate stressful experiences more successfully and with less anxiety.

Avoidance coping can emerge early in a child's development. Infants displaying more behavioral inhibition (a pattern of behavior involving withdrawal, avoidance, and fear of the unfamiliar) have shown increased risk for childhood anxiety [95], and children labeled as inhibited at age three were more likely to develop depression later in childhood [96]. Thus, early behavioral inhibition in childhood may exacerbate risk for internalizing problems in subsequent development. Avoidant coping can also take the form of social withdrawal, especially in youth experiencing depression [97]. Indeed, one study found that social withdrawal in adolescents predicted not only depression, but also future suicide attempts [98].

In addition to avoidance coping strategies, research has suggested emotion dysregulation, or the inability to control emotion expressivity while experiencing negative feelings or experiences, as another shared deficit in childhood anxious and depressive disorders. For instance, one study found that, compared to their non-anxious peers, children with anxiety disorders exhibited more dysregulated management and less adaptive emotion regulation coping when experiencing anger, sadness, and worry [99]. Further, relative to mothers of non-anxious youth, mothers of the anxious children reported that their children were more dysregulated. Cross-sectional studies have indicated that emotion dysregulation of both sadness and anger was related to symptoms of anxiety and depression in elementary school students [100, 101].

Research has also identified emotion regulation coping as a shared aspect of anxious and depressive disorders in youth. For instance, Garber and colleagues found that, while depressed children were more likely to use negative behaviors, such as aggression, to manage negative emotions, nondepressed youth tended to choose more problem-focused and distraction strategies [102]. These general findings have been replicated in subsequent studies examining anxious and depressed youth [103, 104]. Thus, findings suggest that both anxious and depressed youth experience difficulties in coping with negative emotional states.

Additionally, youth with anxiety and depression may share difficulties engaging in cognitive flexibility: the ability to shift one's thinking about a situation in order to alter its emotional salience [92]. Studies suggest that depressed and anxious youth routinely experience negatively biased cognitions, which impair cognitive flexibility. For instance, compared to healthy controls, youth with depression and anxiety tend to report a more pessimistic attributional style: that is, they tend to view their live events as due to causes that are stable, or unchangeable; that reflect personal fault, rather than external causes; and that apply to all aspects of their lives [105, 106]. Further, longitudinal, prospective studies have found that pessimistic attributional style predicts the emergence of both anxiety [107] and depression [108] in youth.

Gender

Female gender might also confer risk for anxiety and depression in youth. By age six, girls are twice as likely as boys to have experienced an anxiety disorder, and this imbalance persists throughout adolescence [109, 110]. Recent research has especially emphasized gender discrepancies in the prevalence of depression [111-113]. During adolescence, girls develop depression at far higher rates than boys [6; 114, 115], and this gender difference continues throughout adulthood [116]. Further, comorbidity of anxiety and depressive disorders is more common in girls than boys [117]. One study found lifetime comorbidity rates of 74.5% for women but only 64.5% for men [118]. Studies have also suggested that sequential comorbidity of anxiety and depressive disorders occurs more commonly among girls [118-120]. For instance,

a longitudinal community study by Costello and colleagues [121] found that though risk for depression following a childhood anxiety diagnosis was high for both genders, it was significantly greater for adolescent girls. Accordingly, it has been suggested that gender differences in anxiety might contribute to the increased risk of depression in females [24].

It is also notable that several of the possible risk factors discussed, including worry, rumination, and emotion dysregulation, might be more common in girls and therefore especially pertinent to girls' anxiety and depression in girls than in boys. For instance, research has found that adolescent girls engage in worry and rumination more frequently than adolescent boys [122]. Separately, research on emotion socialization suggests that emotion dysregulation may be more prevalent and damaging for girls than for boys. As adults, women report experiencing, expressing, and valuing emotion more than men [123], and developmental studies corroborate that parents discuss emotions—especially sadness—more with preschool-aged daughters than with sons [124]. Thus, it has been suggested that girls learn early on to focus more on their emotional states, engage in more emotion-based coping, and are more likely than boys to develop a self-concept as a person who experiences negative affect [125]. For example, girls report engaging more than boys in co-rumination with peers, which involves high levels of discussion of and speculation about problems and negative feelings. This tendency to co-ruminate has predicted girls' higher levels of depression and anxiety symptoms in late childhood and adolescence [126]. Accordingly, girls' heightened concern with and focus on emotional states, both individually and with peers, may precipitate symptoms of both anxiety and depression symptoms during childhood and adolescence [124].

Pathway #3: Anxiety Leads to Depression

As discussed, childhood anxiety may increase risk for developing depression in adolescence. While a causal relationship has not been confirmed, the possibility remains that anxiety leads children to behave and think in ways that precipitate the onset of depression. In investigating this potential link, it is important to note that the disorders' relationship is neither constant nor fully predictable—for instance, not all children with anxiety develop secondary depression. Further exploration of latent risk factors for anxiety and subsequent depression may offer viable answers.

For instance, rumination and worry may not only increase risk for anxiety and depression, but also mediate the shift from primary anxiety to secondary depression. The previously mentioned study by Calmes and Roberts [88] found that worry and rumination contributed to the immediate development of anxiety but not depressive symptoms. Perhaps initial increase in anxiety would precipitate further increases in worry and rumination (in a negative feedback loop), which, in turn, would increase likelihood of developing secondary depression. Such a process would occur in two stages: first, a baseline level of worry and rumination would precipitate initial anxiety symptoms; second, further increases in worry and rumination would lead to depressive symptoms or disorders. While this pathway has not been formally assessed, developmental trajectories suggest its possible utility. Rumination, worry, and anxiety frequently emerge in early or middle childhood, prior to sharp increases in depressive symptoms during adolescence [17]. Consistent with this developmental sequence, repetitive thoughts in early childhood might trigger anxiety in predisposed youth; then, such anxiety might magnify initial worrying and perpetuate the ruminative cycle. These intrusive, repetitive thoughts might eventually overwhelm the child and contribute to avoidance, isolation, and a reduced sense of personal and interpersonal competence, which in turn lead into a depressive state by early adolescence. Thus, rumination and worry might first precipitate anxiety in earlier childhood and later, given further increases in repetitive thoughts, mediate the subsequent transition from anxiety to depression.

Like rumination, impairments in coping and emotion regulation skills—or a delay in the development of these skills—might both predict primary anxiety and mediate the link between anxiety and secondary depression. Deficits in emotional coping are significantly linked with levels of anxious and depressive symptomatology [89]. This result complements findings that youth experiencing internalizing disorders more frequently engage in maladaptive strategies of emotion regulation [78, 81]. Thus, poor coping skills might (1) trigger primary anxiety disorders, (2) prompt increased use of maladaptive coping strategies, and (3) lead to secondary depression. In support of this possibility, research has shown that youth experiencing anxiety symptoms or disorders often believe that they will be unsuccessful in managing emotionally salient experiences [20]. As a result, when faced with such experiences, they may assume their own inadequacy and refrain from trying alternative, adaptive coping strategies. As they find their habitual strategies ineffective, they may ultimately give up and begin experiencing depression. Thus, maladaptive coping and emotion regulation skills may lead to the onset of primary anxiety, and further impairments in these skills may facilitate the onset of depression.

This process may be driven, in part, by shared physiological and neurobiological processes in anxiety and depression, especially among youths experiencing adversity. Stressful childhood experiences might prompt dysregulated HPA activity and amygdala function, placing youth at greater risk for developing impaired emotion regulation skills. If environmental stress persists, dysregulated HPA and amygdala function may be reinforced, creating greater emotion dyregulation over time—and perhaps, ultimately, hopelessness or anhedonia. Thus, biological processes may interact with cognitive emotion regulation abilities and environmental stress to precipitate early anxiety, and in turn, secondary depression.

Researchers have also suggested that social anxiety disorder (SAD) may lead to secondary depression through unique mechanisms. For example, Kessler and colleagues [128] suggested that anxiety disorders impairing an individual's functioning in one or more areas most strongly predict the onset of major depressive disorder. Accordingly, avoidance behaviors triggered by SAD may have strong depressogenic effects. Individuals with SAD often engage in

dysfunctional interpersonal behaviors in attempts to avoid negative social evaluations. However, these behaviors may cause the very rejection that socially anxious individuals hope to avoid. A similar possibility has been suggested by Seligman and Ollendick [8]: anxious youths may experience difficulty in social functioning, which may lead to higher levels of peer rejection. Over time, this rejection may precipitate further social withdrawal and depression in youth. In a similar respect, perhaps especially among youth with SAD, anxiety-induced withdrawal may weaken friendships and lead to loneliness or rejection, increasing hopelessness and ultimately depressive symptoms.

DISCUSSION AND FUTURE DIRECTIONS

Evidence has strongly supported childhood anxiety as a risk factor for adolescent depression, and long-term follow-up studies of childhood anxiety treatments offer preliminary support for a causal anxiety-depression link. However, despite higher rates and sequential comorbidity of anxiety and depression, mechanisms underlying this relationship remain largely unexplored. The present review aimed to synthesize extant literature supporting this particular pathway to developing depression, while highlighting areas of need and challenges in understanding the sequentially comorbid anxiety and depression in youth. Such knowledge might carry important implications for optimized depression prevention strategies: specifically, childhood anxiety treatments may yield decreases in secondary depression.

Limitations

The present review is not without limitations. There exist several challenges to measuring comorbidity between anxiety and depression in youth, which may limit the conclusions that can be drawn from past research. First, anxiety disorders and their symptoms are highly multifaceted. Thus, studies which assess only particular kinds of anxiety—or which attempt to group several anxiety disorders together—may provide imprecise and inaccurate estimates of comorbidity with depression [23, 20]. Second, subdiagnostic symptoms are often not assessed in comorbidity studies focusing on youth anxiety and depression [20]. Thus, the prevalence and consequences of subdiagnostic *symptoms* of anxiety and depression is likely under-reported and relatively unknown. One community-based study that did assess subclinical impairment found that 5-10% of youth reported subclinical anxiety or depression symptoms at any given time, and that such symptoms were associated with considerable psychosocial impairment [129]. Another recent study found strong high levels of comorbid internalizing symptomatology—though not necessarily diagnoses—among youths with OCD and depression. Future research should assess the nature of risk conferred by subclinical symptoms, both in the presence and absence or clinically significant problems [130]. A third limitation results from the fact that rates of anxiety and depressive disorders are likely to vary according to age and developmental period. Such changeability makes rates of co-occurrence or symptom clusters difficult to track between childhood and adolescence [20].

Finally, much of the reviewed literature is cross-sectional rather than longitudinal, limiting discussion of possible pathways relating youth anxiety and depression. In the absence of longitudinal risk factor studies assessing symptoms of both disorders, we can claim only that certain risk factors predict both disorders—not that one disorder emerges before the other, given a particular profile of risk. Future research in this area may enable a more comprehensive assessment of mechanisms by which specific factors may precipitate sequential comorbidity of anxiety and depression in youth.

In light of these limitations and of the literature reviewed, several research and clinical strategies may help broaden understandings of the anxiety-depression link and inform assessment and treatment of internalizing disorders in youth.

Suggestions for Research and Practice

Assess Depression and Anxiety Symptoms (not Just Diagnoses)

Investigators have inconsistently addressed sub-threshold symptoms in reporting prevalence rates and program outcomes. However, children and adolescents may be highly symptomatic without qualifying for an anxiety or depressive disorder, and certain symptom clusters may be equally debilitating as a full diagnosis. Thus, researchers should more closely consider both symptoms and diagnoses of participants—particularly when assessing intervention effects.

Incorporate Longitudinal Diagnostic Assessment in Clinical Contexts

Given strong evidence for sequential comorbidity of anxiety and depression in youth, longitudinal approaches to diagnostic assessment might prove useful for clinicians working with children and adolescents. Given the dynamic nature of these diagnoses, viewing them along a possible continuum might guide clinicians' care and choice of treatment. This approach might be especially useful for children exhibiting one or more shared risk factor for anxiety and depression, such as high worry or rumination, avoidance coping, or a genetic predisposition suggested by family history.

Consider Developmental Relevance of Longitudinal Measures

Further, the longitudinal nature of exploring causal links has complicated reports of program outcomes and comorbidity rates. Researchers have suggested that, as child participants age across interventions' follow-up periods, or during assessment points in epidemiology studies, measures used at baseline may eventually grow inappropriate for participants' developmental levels [4]. While some child measures couple to adult variations, even measures intended for youth were not designed to assess shifts across developmental stages. Further, certain disorders, such as specific phobias and separation anxiety, tend to decline after middle childhood, rendering their measurement less relevant by adolescence. This issue points to the utility of dimensional constructs (i.e. clinical/diagnostic interviews), in addition to self-report measures, to assess participants' symptoms over periods of long-term follow-up—especially those that coincide with

major developmental transitions. Future studies should actively address these concerns.

Standardize Term Utilization: 'Correlate' vs. 'Risk Factor' vs. 'Causal Risk Factor.'

Researchers may further improve knowledge of the anxiety-depression link by standardizing terminology regarding correlates, risk factors, and causal risk factors. While Kraemer and colleagues [25] provide effective definitions for these terms, researchers have variably adhered to these criteria. Correlates and risk factors are routinely mislabeled, causing inconsistency across intervention literature and obscuring valuable findings. If investigators used standard terminologies more consistently, support for the anxiety-depression link—and, more broadly, for research on risk factors in general—will become more accessible, relatable, and utilizable.

Parse Causal Links by Conducting Longitudinal and Intervention Studies

Additionally, future research should aim to assess more thoroughly whether childhood anxiety does, in fact, cause adolescent depression. Longitudinal studies on the development, persistence, and comorbidity of anxiety and depression over time—beginning in early childhood, for instance, and continuing through adolescence—may forward this objective. By including multiple assessment points, these studies may facilitate identification of mediators and moderators of the anxiety-depression link across youth development. Thus, longitudinal research may help disentangle complex relations between anxiety and depression over time, such as those proposed in Fig. (**1**).

Another way for researchers to test a potentially causal link may be to assess long-term intervention outcomes—both primary and secondary—of youth treated for anxiety symptoms or disorders. Only a few such investigations currently exist: most intervention outcome studies do not continue assessments beyond post-intervention. By prospectively assessing whether treating childhood anxiety decreases adolescent depression over multi-year timeframes, intervention studies might provide insight towards understanding a possibly causal anxiety-depression link.

However, it remains possible that future investigations may not be able to conclusively confirm early anxiety as a causal risk factor for secondary depression. Some researchers have suggested such a task might prove impossible [4]. Nonetheless, childhood anxiety remains an established risk factor for depression in adolescence, and unified treatment-prevention programs might effectively reduce both present anxiety and future depression in youth. In order to facilitate the creation of such programs, research must establish not only the presence of an anxiety-depression link, but also the pathways that mediate and moderate this relationship. Knowledge of underlying mechanisms can inform interventions that target variables most relevant to the anxiety-depression link, increasing program specificity and effectiveness.

Assess Moderators of Anxiety-Depression Link

Pathways might be identified in several ways. First, longitudinal studies might assess moderators of sequential anxiety-depression comorbidity across childhood and adolescence. For instance, among children with anxiety symptoms, those with genetic risk factors or exposure to early adversity might be more likely to develop subsequent depression. Additionally, research might assess moderators of the impact of anxiety interventions on depression outcomes—for instance, gender [131]. Although few studies have investigated potential moderators of preventive depression interventions, doing so may specify groups that benefit most from a given intervention and direct more precise intervention efforts. For instance, one question that has been under-examined in prior anxiety intervention research is whether specific anxiety diagnoses at baseline (e.g. SAD, GAD) differently impact long-term anxiety and depression outcomes. This area of inquiry might inform diagnosis-specific programs for both early anxiety and secondary depression.

Assess Mediators of Anxiety-Depression Link

Both etiological and intervention research should address mediators underlying the relationship between anxiety and depression. Longitudinal studies with multiple measurement points are uniquely equipped to assess mediators of the anxiety-depression link. Such studies can assess whether factors such as worry, rumination, or coping skills might influence the shift from early anxiety to later depression. Separately, only a small minority of childhood anxiety intervention studies report meditation analyses, and even fewer have found positive results. However, research exploring the factors that might drive the shift from anxiety to depression might highlight key intervention components. As discussed, potentially relevant mediators include increases in rumination and worry, as well as decreases in emotion regulation and coping skills. Future intervention studies should assess these factors' influences on symptom reduction and prevention.

CONCLUSION

Pathways relating anxiety and depression in youth are complex and multidirectional, dependent upon a litany of influences across development. It is unlikely that any sole mechanism or risk factor fully accounts for the disorders' sequential comorbidity. Nonetheless, longitudinal etiological studies, as well as research on the treatment and prevention of internalizing symptoms, should actively pursue more accurate understandings of relations between youth anxiety and depression. Particularly needed are rigorous explorations of (1) the utility of treating childhood anxiety to prevent adolescent depression, and (2) the mechanisms underlying the possible anxiety-depression link over time. While research may ultimately fall short of establishing a causal link, understanding shared risk factors and mechanisms connecting anxiety and depression in youth remain crucial for improved assessment, treatment, and prevention efforts. To accomplish this goal, future research should assess long-term secondary outcomes of childhood anxiety treatments, as well as outcome mediators and moderators of the sequentially comorbid anxiety-depression relationship. Through these and other avenues (see Table **1**), investigations can work towards a unified protocol to treat and prevent internalizing disorders, combating some of the world's most prevalent mental health problems.

Table 1. Summary of Research and Practice Suggestions

Measurement	Clinical Assessment	Intervention Evaluation	Exploring Mechanisms
• Assess sub-threshold symptoms as well as diagnoses in comorbidity, outcome research • Consider developmental relevance of measures in longitudinal studies • Explore links of specific anxiety disorders to secondary depression in youth	• Consider longitudinal approaches to diagnostic assessment, especially for youth with supported risk factors for anxiety or depression	• Examine long-term outcomes of child anxiety treatments on adolescent depression	• Assess moderators of child anxiety treatments' effects on adolescent depression (e.g., specific anxiety diagnosis) • Test possible mediators of anxiety-depression link through longitudinal studies (e.g. increased worry/rumination, decreased coping skills, gender differences)

CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest pertaining to this submission.

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