Anxiety And Depression Journal

SCIENTIFIC LITERATURE

Special Issue Article "Depression"

Review Article

Adolescent Depression: A Narrative Review

Tiffany Field

Departments of Pediatrics, Psychology, and Psychiatry, University of Miami/Miller School of Medicine, USA

ARTICLE INFO

Received Date: December 12, 2021
Accepted Date: January 04, 2022
Published Date: January 07, 2022

KEYWORDS

Adolescent depression
fMRI
Cognitive behavior therapy

Citation for this article: Tiffany Field. Adolescent Depression: A Narrative Review. Anxiety And Depression Journal. 2022; 3(1):118

Corresponding author:
Tiffany Field,
Departments of Pediatrics, Psychology, and Psychiatry, University of Miami/Miller School of Medicine, USA,
Email: tfield@med.miami.edu

ABSTRACT

This narrative review is based on adolescent depression research published over the last 5 years and located on PubMed and PsycINFO. It includes studies that could be categorized as depression effects, risk factors, biomarkers and interventions. The effects include negative social interactions, negative emotions, inferior academic performance, and somatic complaints including headaches and disturbed sleep as well as comorbid disorders including internet addiction, victimization, drug use and suicidality. Intrapersonal risk factors include negative thinking and self-evaluation and interpersonal risk factors include maternal depression and peer rejection. The biomarker studies featured in this recent research include electrodermal activity, cortisol, pro-inflammatory cytokines, and fMRI data on frontal limbic system connectivity during rest and in response to sad and angry faces. Genetic markers include DNA methylation and both short and long serotonergic alleles. Interventions include cognitive behavior therapy, interpersonal therapy, family therapy, internet therapy, school based programs, lesser known therapies like "thinking about reward" and "specifically targeting depression". Physical therapies include transcranial magnetic stimulation and exercise. Limitations of the literature include the frequent reliance on self-report and parent report and the univariate/unidimensional nature of the studies focusing on a single effect, risk factor, biomarker or intervention. Multivariate longitudinal studies are needed as well as research that compares different types of prevention and intervention therapies.

INTRODUCTION

This narrative review is based on adolescent depression research published over the last 5 years (2014-2019) and located on PubMed and PsycINFO. The terms adolescent depression were entered and exclusion criteria were case reports, qualitative studies and foreign language papers. This search yielded 92 papers including randomized controlled studies, systematic reviews and meta-analyses. These were then categorized as studies on depression prevalence, effects, risk factors, biomarkers, genetic markers and interventions. The prevalence is relatively high and variable across countries. The effects include negative social interactions, negative emotions, inferior academic performance, and somatic complaints including headaches and sleep disturbances as well as comorbid conditions including internet addiction, victimization, drug use and suicidality. Risk factors include negative thinking and self-evaluation and interpersonal factors include maternal depression and peer rejection. The biomarkers that have been recently studied include electro dermal activity, cortisol, pro-inflammatory cytokines, and fMRI scans focused on frontal limbic system

connectivity during rest and in response to sad and angry faces. Genetic markers include DNA methylation and both short and long serotonergic alleles. The intervention studies include cognitive behavior therapy, interpersonal therapy, family therapy, internet therapy, school based programs, and lesser known therapies like "thinking about reward" and "specifically targeting depression". Physical therapies include transcranial magnetic stimulation and exercise. Limitations of the literature are the frequent reliance on self-report and parent report as well as the univariate/unidimensional nature of the studies focusing on a single effect, risk factor, biomarker or intervention. Multivariate longitudinal studies are needed as well as research that compares different types of prevention and the various therapies. This narrative review is accordingly divided into sections on these topics. In these sections, brief descriptions are given on the research findings as well as the methodological limitations.

PREVALENCE

The prevalence of adolescent depression is relatively high, although it varies across countries. In the National Survey on Drug Use and Health (N= 95,856 adolescents), the prevalence of adolescent depression increased steadily from 8.3 to 12.9% over the years 2011 to 2016 [1]. In that survey, higher rates of depression were noted for females, older adolescents and single-mother families. Less authoritative parenting and negative school experiences predicted adolescent depression. Negative school experiences also increased the chances of the adolescents using treatments and medication. A similar prevalence has been noted among Arab adolescents from Jordan at 15% [2]. In this sample (N=2349) based on the Beck Depression Inventory, 34% of the sample reported moderate to severe depression. Depression scores were higher for females, ages 14-15 and living in low income families. The prevalence of depression was much higher in a smaller sample of Tunisian adolescents (N=386 adolescents) [3]. Based on the Beck Depression Inventory, the prevalence was 76%. Of the depressed students, 39% had mild depression, 49% had moderate depression and 21% had severe depression. The incidence was greater for females and for the first and fourth graders. Other risk factors were low and medium SES, school dissatisfaction and comorbidity with anxiety. Comorbidity occurred in 86% of students. Surprisingly, comorbidity of depression and anxiety has rarely been reported in this recent literature, and depression has rarely been broken down by severity as it was in this study (Table 1).

Table 1: Prevalence of adolescent depression.

Prevalence	Location	First Author
13%	U.S.	Lu
15%	Jordan	Dardas
76%	Tunis	Sendi

DEPRESSION EFFECTS

The studies that have been classified here as depression effects were derived from cross-sectional samples as opposed to longitudinal samples, so directionality could not be determined, i.e. it is not clear if they are effects/symptoms or risk factors/predictors and they may be bi directionally related to depression. The adolescent depression papers that were classified as effects studies include those focused on social interactions, emotional states, somatic complaints, academic performance, comorbid disorders, adult depression and suicidality. Although all these factors could be concurrent and/or interactive, most of the studies have been univariate (Table 2).

Table 2: Effects of adolescent depression.

Effects	First Author
Parent-adolescent interactions	
<Time in matched interaction states	Hollenstein
>Sympathetic activity	Nelson
>Parent anger and adolescent dysphoria	Bodner
Emotional effects	
>Pessimism, sadness, loneliness & self-hatred	Mullarkey
Somatic Complaints	
Fatigue & headaches	Nardi
Migraine headaches & poor health	Naicker
Sleep disturbances	Urrila
Academic performance	
Achievement	Park
GPA	Respress
School completion	Clayborne
Comorbid problems and adult depression	
Internet addiction	Field [15], Yang
Suicidality	Field [19], Marsh
Victimization	Davis
Substance abuse	Mcleod
Cannabis use & Alcohol use	Rhew
Adult depression	Johnson
Suicide risk	Akca

Social interactions

At least three social interaction studies appeared in the recent literature on adolescent depression. They are unique to the literature inasmuch as they are not simply dyadic interaction studies but feature the adolescent interacting with both parents.

Different methodologies have been used in the three studies, although they have yielded similar results. The findings suggest that the interactions of depressed adolescents and their parents are more negative than those of non-depressed adolescents and parents.

In one parent–adolescent interaction study, a state space grid analysis was used to characterize the simultaneous states of the individuals in the triadic family interactions [4]. This analytic technique is based on dynamic systems principles and provides graphics of real-time trajectories that capture the content and sequence of interaction behavior. This analysis yields quantitative data on the discrepant and matching states and on the diversity, flexibility and predictability of behaviors. The authors reported that the depressed adolescent triads spent more time in discrepant affect states and less time in matched affect states. In addition, they were less predictable about their affect and displayed a wider range of affect. In a subsequent publication, this research group reported data on multiple methods including self–report on affect, behavior observations and psychophysiology [5]. In this study, 152 adolescents and their parents were asked to discuss positive and negative aspects of the relationship and to reminisce on positive and negative memories. Once again this group found less positive or negative affect but also greater sympathetic activity in the depressed adolescents' interactions with their parents. More aggressive behavior during these interactions was accompanied by parasympathetic withdrawal. In still another paper by this group, a network analysis was used to assess the temporal sequencing of affective behaviors during the interactions of depressed adolescents and their parents [6]. This analysis uses sociograms in which behaviors are represented as points and relationships between them as lines. Parents' angry behavior and adolescents' dysphoric affect followed each other more often in the depressed adolescent interactions. A similar network analysis study is reviewed in the next section on the emotional effects of adolescent depression.

Emotional effects

In this network analysis on Children's Depression Inventory scores (N=1409), the most central symptoms in the network were pessimism, sadness, loneliness and self–hatred [7]. Significant associations were noted between symptoms including sadness–loneliness; sleep disturbance–fatigue, sadness–crying and self-hatred-negative body image. The latter association was noted in females more than males. These associations were assessed for their stability and accuracy which were noted to be robust. Some of these symptoms have been noted in research reviewed in the following section on somatic complaints including fatigue and sleep disturbances.

Somatic complaints

In a review of the literature on adolescent depression symptoms, the most frequent somatic complaints were fatigue and headaches [8]. Irritability was also noted most frequently in females and was related to the severity of depression. In a study on 1027 adolescents from the National Population Health Survey, measures were taken every two years from age 16 to 27 [9]. Migraine headaches were among those symptoms that persisted after 10 years. Others included recurrence of depression, low levels of social support and poor self–reported health.

Sleep complaints have been prevalent among depressed adolescents, and disturbed sleep and depression are thought to be bidirectionally related [10]. However, the findings for both self–report data and from polysomnographic studies are mixed. For example, in a naturalistic follow-up study on 166 adolescents, self-reported sleep complaints were less frequent at the one-year follow-up than they were at baseline, and the complaints at baseline did not affect the clinical outcome. Surprisingly, the severity of sleep complaints at baseline was associated with greater improvement of depression symptoms over time. Some have suggested similarities between adolescents and adults who are depressed including sleep onset difficulty and abnormalities in REM sleep [10]. Since sleep is naturally changing during adolescence with a circadian shift toward "eveningness", sleep may not be a good marker for depression during adolescence. Sleep disturbances would, in turn, be expected to negatively affect academic performance.

Academic performance

Low academic achievement has been associated with both sleep dissatisfaction and depression in adolescents. For example, in a study on 75,066 middle and high school students in South Korea, adolescent depression was related to both self-reported sleep dissatisfaction and to self-rated academic achievement [11]. And, in another large sample study, a

relation between depression and academic performance was noted [12]. However, in this longitudinal database, GPA was a significant predictor of depressive symptoms instead of the reverse across three racial groups (Black, White and Other minority adolescents). This finding again highlights the bi directionality of adolescent depression and other problems like inferior academic performance. Another illustration of bi directionality of adolescent depression and co-morbid problems is noted in a study on internet addiction in adolescents [13]. In at least one study, several negative performance effects were noted including failure to complete school and to secure employment highlighting the several comorbid problems of adolescent depression [14].

Comorbid problems and adult depression

Comorbid problems that have been associated with adolescent depression in the recent literature include Internet addiction, aggression and victimization, drug use and suicidality [15,16]. In a study on a sample of 3507 adolescents in China, path analyses suggested that internet addiction effects on adolescent depression were notably mediated by life events [13]. Although there are many studies documenting Internet addiction effects on depression, the reverse direction of effects with depression leading to Internet addiction has rarely been noted [15]. In contrast, depression has been noted to lead to victimization, while victimization did not lead to depression in a large sample of high school students (N=3793) [17]. Surprisingly, there were reciprocal effects between aggression and victimization in this sample, but aggression was not related to depression. In another path analysis study, victimization and depression were comorbid problems mediated by academic achievement [18].

Illicit substance abuse has been associated with adolescent depression in at least two studies in this recent literature. In a New Zealand sample of 1265 adolescents, the severity of depression based on DSM symptom criteria was related to illicit substance abuse/dependence [19]. In a study on adolescents from Seattle (N=521), 21% of the sample had cannabis use disorder and 20% had alcohol use disorder [20]. Surprisingly, only the cannabis disorder was related to adolescent depression, and no gender differences were noted.

In a recent systematic review based on MEDLINE and PsycINFO databases, the authors noted that 17 of 18 articles on adolescent and adult depression showed a significant association with depressed adolescents having 2.78 times the odds of later having adult depression [21]. In addition, seven of eight studies on adolescent depression and adult anxiety noted a significant association and three of five studies documented a significant association between adolescent depression and adult suicidality. Depressed adolescents have also continued being depressed in adulthood when they have lived with separated parents. In a study on adolescents and young adults (N=348), significant relationships were noted between suicide risk as assessed by the Suicide Probability Scale and depression as well as anxiety. Other risk factors that emerged in this study included education, psychiatric treatment, self–harm, and smoking and drinking.

RISK FACTORS

The recent literature on risk factors for adolescent depression can be classified as intrapersonal or interpersonal risk factors. The intrapersonal risk factors include female gender, negative thinking, and internalizing behavior. The interpersonal risk factors include maternal prenatal stress, maternal depression, maternal hostility, less paternal support, peer rejection and relational challenges (Table 3).

Table 3: Risk factors for adolescent depression.

Risk & factors	First Author
Intrapersonal	
Females >depressed	Dardas [2], Lu,Sendi, McGuinness
Negative thinking	Rawal, Orchard,Auerbach
Externalizing/internalizing behavior	Weeks
Interpersonal	
Prenatal stress	Maxwell
Maternal depression	Monti
Paternal depression	Lewis
Mother-Adolescent interactions	Gate, Lewis [31]
Peer rejection	Platt, Silk
Peer rejection	Stikkelbrook, Nishi, Kawa, Lewis [36]

Intrapersonal risk factors

Female gender: Female gender is one of the most frequently reported risk factors for adolescent depression as has already been noted above in at least three recent prevalence studies [1-3]. This gender disparity emerges during adolescence when adolescent girls have approximately twice the rate of depression as compared with boys [22].These authors have attributed greater depression in adolescent girls to their tendency to ruminate.

Negative thinking/self-criticism: In a sample of 252 adolescents, those with previous and current depression had

faster reaction times to dysfunctional attitudes presented to them on a computer survey [23]. The faster reaction times to dysfunctional attitudes were also associated with later depressive symptoms, but only for older adolescents. The authors concluded that faster reaction time to endorsing dysfunctional attitudes may be a risk factor for future depression. However, this sample could be considered biased and unrepresentative as the adolescents had family histories of depression. In another sample of adolescents both from the community (N=212) and from a mental health clinic (N=84), negative self-evaluations explained 60% of the variance in depression severity across all participants [24] Once again, causality cannot be attributed to negative self-evaluation as this was a cross–sectional sample. However, in a longitudinal sample (N=157 adolescents), self–criticism was more predictive of depression than depressogenic attributional style [25] and, self-criticism predicted dependent interpersonal but not non-interpersonal stress. The authors suggested that self-criticism is an important risk factor for adolescent depression and that it should be more carefully considered in designing interventions. Surprisingly, no gender differences emerged in this study.

Externalizing/internalizing behavior: In a large longitudinal sample of Canadian youth (N=6425), longitudinal pathways were explored between internalizing problems, externalizing problems and depression [26]. Greater internalizing behavior at age 6-7 predicted greater age 12-13 externalizing behavior and greater age6-7 externalizing behavior predicted greater age 17 depression. These pathways, as the authors suggested, highlight the multi factorial nature of adolescent depression.

Interpersonal risk factors

Prenatal stress: In a longitudinal study on 1711 mother–offspring dyads, maternal narratives were qualitatively coded for themes of prenatal stress [27]. Latent class analysis revealed a high risk group based on pregnancy factors (ambivalence and negativity towards pregnancy as well as higher frequency hassles, less paternal education, greater maternal age and higher pre-pregnancy BMIs). In addition, offspring developmental factors were noted (inferior cognitive function during childhood and adolescence, more severe maternal depression during adolescence, less perceived parental support during adolescence). Both high risk males and females had more depressive symptoms during adolescence.

Maternal and paternal depression: Maternal depression has also contributed to adolescent depression based on a four–year longitudinal study of 165 adolescents [28]. In this research, mothers were given diagnostic interviews and the adolescents reported on responses to peer stress. The highest levels of depression were reported in adolescents who were exposed to maternal depression and who showed maladaptive stress responses (high effortful disengagement and involuntary engagement). Paternal depression was also a significant predictor variable in at least one recent study [29].In this study from Ireland (N=6070 families) and the UK (7768 families), paternal depression was associated with adolescent depression independent of the relationship between maternal depression and adolescent depression. And the magnitude of the relationship between paternal depression and adolescent depression did not differ from that of the mother-adolescent depression relationship.

Mother-adolescent interactions: Rumination has been a mediator variable for the relationship between low levels of positive maternal behavior and depressive symptoms in adolescent girls [30]. In this study on 163 mother–adolescent dyads, adolescents' self–reported depressive symptoms and rumination at ages 12, 15 and17 years. Observations were conducted on interactions between mothers and their adolescents. The data analysis revealed a significant indirect effect of low levels of positive maternal behavior on adolescent female depressive symptoms via rumination. Still more confirmatory data on the relationship between mothers' interaction behaviors and adolescents' depression symptoms were found in another longitudinal community sample of 316 dyads [31]. In this sample, a longitudinal bidirectional relationship was noted between mother hostility towards their daughters and depression symptoms in the adolescent girls, with reciprocal effects between the daughters and their mothers. Further, they used a sample of 1075 twin pairs (653 dizygotic, 422 monozygotic twins) to assess the genetic versus environmental factors [31]. Based on cross-lagged panel analyses, a significant pathway was found between mother hostility and daughter depression independent of genetic

factors. Surprisingly, a pathway was found between daughter depression and father hostility but not vice versa.

Peer rejection: Peer rejection has also been reciprocally related to depression symptoms during adolescence [32]. Following a comprehensive review of the literature by these authors, they suggested that fMRI–based neural feedback training could be used to modify adolescents' information processing to result in more adaptive responses to peer rejection. As will be seen in the section on brain circuitry, peer rejection is accompanied by increased neural responses during neuroimaging [33], highlighting the importance of this interpersonal risk factor.

Negative life events: At least three studies in the recent literature have reported on negative life events contributing to adolescent depression. In a study on 398 adolescents including 52 depressed outpatients who all reported stressful life events, path analyses were used to test mediation variables for the relationship between life events and depression in adolescence [34]. The notable life events that were related to depression in this sample were health threats and relational challenges. These, in turn, were mediated by maladaptive strategies which in this case were self–blame, catastrophizing and rumination. Surprisingly, no mediation effects were found for adaptive strategies.

In a study from Japan on non-clinical adolescents (N=1038), the type and timing of negative life events that were associated with adolescent depression were explored [35]. These researchers' findings suggested that negative life events that occur at a younger age resulted in more negative outcomes and that negative life events timing and intensity were associated with current symptoms of depression. Path analysis revealed that the relationship between perceived stress at the time of negative life events was a direct and an indirect predictor of current depression and that these, in turn, were mediated by posttraumatic stress symptoms and posttraumatic growth. Female gender was also a mediator in their data analysis. Others have also referred to negative early life events as a risk factor for depression in adolescent girls in particular and a hormonal biomarker as a risk factor for depression in boys [36]. These authors reached this conclusion based on their review of the findings from the longitudinal ROOTS study.

BIOMARKERS

Potential underlying biological mechanisms (called biomarkers here) that have appeared in the recent literature on adolescent depression include reduced heart rate variability, electro dermal hypoactivity, altered pupillary light reflex at least in the left eye, slow cortisol recovery following a social stressor and elevated pro-inflammatory cytokines. These all reflect a sympathetic/parasympathetic imbalance. The electro dermal hypoactivity and pupillary light reflex are notable measures of sympathetic activation. Sympathetic activation, in turn, could lead to or be associated with delayed cortisol recovery and with elevated pro-inflammatory cytokines. Unfortunately, these results were derived from univariate as opposed to multivariate studies that, in turn, would be needed to inform relationships between these biomarkers (Table 4).

Table 4: Biomarkers for adolescent depression.

Biomarkers	First Author
Electrodermal hypoactivity	Mestanikova [38]
Altered pupillary light reflex	Mestanikova [39]
Delayed cortisol recovery	Stewart
Elevated pro-inflammatory cytokines	Pallavi [44]
Lower neurotrophic factors	Pallavi [45]

Reduced heart rate variability

Depression has been associated with sympathetic control in adults but has rarely been assessed in adolescents. Exceptions are studies on reduced heart rate variability, electro dermal hypo activity and altered pupillary light reflex in adolescents by the same research group. In their most recent paper, heart rate variability was studied in response to a stress protocol in adolescents with major depression [37]. In this study, heart rate was recorded in 60 depressed adolescents and 60 matched controls during baseline, a Go/No-go test, recovery, a supine position and standing up. In each of these phases the depressed adolescents had significantly reduced heart rate variability indicating abnormal neurocardiac reflex functioning.

Electrodermal hypoactivity

In another study by the same group, sympathetic control was suggested by electrodermal hypoactivity in 25 depressed adolescent girls [38]. These girls without comorbidities and pharmacotherapy were matched with healthy control adolescent girls. The electrodermal activity of the depressed adolescents was significantly lower than that of their non-–

depressed controls. As the authors suggested, dysfunctional regulation of the sympathetic autonomic nervous system could be a potential "pathomechanism" for negative health outcomes in depressed adolescents.

Altered pupillary light reflex

In still another study; the same research group assessed altered pupillary light reflex as another index of sympathetic/parasympathetic imbalance. This was demonstrated at least for the left eye in 25 depressed adolescent girls [39]. The data on this measure suggested that the average constriction velocity and the maximum constriction velocity for the left eye were lower in the group of depressed adolescent girls. No differences were noted on the right eye. This finding may relate to the contralateral excessive right frontal EEG activation noted in depressed individuals [40]. Although this measure is typically reflective of excessive sympathetic activity, the authors refer to it as deficient parasympathetic activity. Lower parasympathetic activity (vagal activity) as well as right frontal EEG has been reported for depressed individuals (e.g. [40]. However, it would be important to assess all three of these measures on the same sample. It's not clear whether there would be a gender difference on these measures. In addition, the electrodermal hypoactivity and altered pupillary light reflex results derive from an exclusively female adolescent sample. If female adolescents were more severely depressed than male adolescents, as they have been in other samples (e.g. [22], those functions might be more abnormal in females.

Delayed cortisol recovery following a social stressor

Delayed cortisol recovery following a social stressor is another biomarker of adolescent depression. In a study on depressed and non-depressed adolescents, the change in saliva cortisol between the peak outputs at 25 minutes post-stressor versus the sample assayed for the recovery period (65 minutes post-stressor) was assessed [41]. Delayed post–stressor cortisol recovery was noted in the depressed adolescents who had high scores on rumination whereas those who were high on distraction and problem-solving had more rapid cortisol recovery. These data are consistent with literature suggesting that rumination is a central cognitive construct in depressed individuals [42]. The mechanism thought to underlie rumination's effect is the inability to shift focus away from negative stimuli. Ruminating about the negative stressor may contribute to the delayed cortisol recovery.

Elevated pro-inflammatory cytokines

Given the data on sympathetic dominance of autonomic nervous system activity and the slow recovery of cortisol response to stress, pro-inflammatory cytokines might also be elevated as they have in other samples (e.g [43]. Pro-inflammatory cytokines have been assayed in depressed adolescents [44]. In this study, 77 depressed adolescent patients who were medication free were compared to 54 healthy controls. The depressed adolescents had significantly higher levels of the pro-inflammatory cytokines IL–2 and IL–6. On comparing the medicated versus non medicated patients, IL–2 and TGF–beta-1 were elevated in the medicated groups, suggesting that medication was a confound in the study. Also, as mentioned earlier, females who often have more symptoms of depression might be expected to have more elevated pro-inflammatory cytokines.

Lower neurotrophic factors

Similarly, in a study by the same group of investigators, but on neurotrophic factors, depressed adolescents had significantly lower levels of Brain Derived Neurotrophic Factors (BDNF) [45] Once again; the gender bias suggested that female adolescents had significantly lower levels of all neurotrophic factors.

BRAIN REWARD CIRCUITRY

Functional magnetic resonance imaging (fMRI) data indicate that depressed adolescents show abnormal neural functioning both in terms of activation and conductivity and both at rest and in response to emotional stimuli [46]. Adolescence is a peak period for the onset of depression as well as the development of brain reward circuitry [47]. These authors have proposed three separate but related etiological models for reward dysfunction in depressed adolescents. In the first model, acute and chronic stresses are seen to contribute to reward deficits that in turn lead to depressive symptoms. In the second model, reward–related dysfunction is seen as generating stress, especially interpersonal stress which then leads to depressive symptoms. While the second model is the reverse direction of the first, the third model, a diathesis–stress model combines the first two, addressing the interaction between reward dysfunction and stress and its contribution to depression. The

following studies have used fMRI data and other neuroimaging technology to assess resting reward circuitry followed by studies using fMRI data to assess responses to emotional stimuli (Table 5).

Table 5: Brain reward circuitry in adolescent depression.

Resting State	First Author
Abnormal neural functioning	Kovacs, Auerbach
Abnormal ventral striatum connectivity	Goff [48], Pan
Hypoactivity nucleus accumbens	Goff [49]
Amygdala –frontal connectivity deficits	Cullen, Connolly
Abnormal prefrontal cortex-hippocampus	Geng
Hypoperfusion frontal & limbic regions	Ho
FMRI responses to emotional stimuli	
Decreased activity to sad and fearful faces	Ho
Greater activation when ignoring fearful faces	Colich
Increased activation to peer rejection	Silk

Neuroimaging during a resting state

Most of the neuroimaging studies have implicated abnormal connectivity between reward structures in the limbic system and the frontal cortex. These structures have included the ventral striatal area, the nucleus accumbens, the amygdala and the hippocampal region. Adolescent depression, for example, has been related to early–life adversity and altered ventral striatal development, a limbic structure that is implicated in reward processing [48]. Abnormal ventral striatum functional connectivity has been predictive of depression in a community sample of 637 children. Depressed adolescents who have experienced early life stress have also shown hypoactivity of the nucleus accumbens, a limbic structure associated with reward processing and motivation [49]. In this study, lower reactivity was correlated with higher depression scores. Amygdala–frontal connectivity deficits have been noted in a study on 41 depressed adolescents and 29 healthy adolescents matched on age and gender [50]. The depressed adolescents showed lower positive resting state functional connectivity between the amygdala and the hippocampus. Connectivity was inversely correlated with general depression/dysphoria and lassitude and was positively correlated with well–being. As the authors suggested, these circuits are important for memory and for physiological responses to emotions.

Further support for altered amygdala resting state functional connectivity has been provided for adolescent depression [51]. In this study, medication–free depressed adolescents (N=48) versus matched healthy controls (N=53) showed reduced amygdala–based resting state functional activity within the dorsolateral prefrontal cortex and the ventromedial prefrontal cortex. This dysfunction of frontolimbic circuits has been suggested as an underlying mechanism for affect integration and depression symptom severity. Another group provided resting state functional magnetic resonance imaging data as well as diffusion tensor imaging in medication free adolescents (N=26) and healthy controls(N=31). [52]. The depressed adolescents showed decreased functional connectivity in four prefrontal cortex regions and abnormal prefrontal cortex–hippocampus neural circuitry. Diffusion tensor imaging has also shown disturbances in tracks related to reward processing in depressed adolescents including the anterior limb of the internal capsule and projection fibers to the orbital frontal cortex [53]. These data provided further confirmation of the disconnect between prefrontal and limbic emotional regions in depressed adolescents. Arterial spin labeling has enabled noninvasive measures of regional cerebral blood flow. This technique was used to examine baseline cerebral perfusion in 25 medication–free adolescents as compared to 26 matched controls [54]. This measurement revealed significant frontal, limbic, paralimbic and cingulate hypoperfusion in the depressed adolescents. The authors argued that dysfunction in these regions may be contributing to the cognitive, emotional and psychomotor symptoms in depressed adolescents. Although they suggest that this biomarker could inform early interventions, arterial spin labeling may be noninvasive but also costly as a screening measure.

Functional mri responses to emotional stimuli

Although most of the fMRI studies are based on resting fMRI data, others have explored functional MRI during memory and emotional stimuli tasks. For example, facilitated memory for negative stimuli has been noted in depressed adolescents in which fMRI data were collected during both encoding and retrieval stages [55]. In a neuroimaging/ emotional face paradigm, 19 medication–free depressed adolescents and 18 healthy controls were scanned during the presentation of neutral, happy, sad and fearful faces [56]. Depressed adolescents showed decreased activity to negative faces (sad and fearful) in prefrontal, cingulate, striatal and limbic regions. In a similar study, fMRI data on depressed versus matched healthy control adolescents were assessed during the

presentation of fearful faces [54]. The depressed adolescents exhibited poor perceptual sensitivity in this task and perceptual sensitivity was negatively correlated with functional connectivity of the subgenual anterior cingulate cortex. Similarly, depressed adolescents have undergone fMRI monitoring while performing an emotional distractor task in which they were asked to ignore fearful, sad or neutral faces [57]. Although depressed and healthy control participants showed equivalent response time and accuracy, the depressed adolescents showed greater activation in the dorsal anterior cingulate cortex when ignoring fearful versus neutral faces. The groups did not differ when ignoring sad faces. Functional neuroimaging has also been conducted with depressed adolescents (N=48) and age and gender matched controls (N=27) during the presentation of acceptance and rejection feedback from fictitious peers in an online peer interaction [33]. The depressed adolescents showed increased activation to rejection in the amygdala, the subgenual anterior cingulate, and the left nucleus accumbens. The depressed adolescents did not differ from the healthy controls in their responses to acceptance. These findings suggest increased reactivity to peer rejection by depressed adolescents. A multivariate study including fMRI, behavioral and self-report data would more conclusively establish negative reactivity to peer rejection by depressed adolescents. These biomarker studies, not unlike the genetic marker studies on depressed adolescents, have not been multivariate.

GENETIC MARKERS

Several genetic marker studies have been conducted with depressed adolescents including the heritability of several depressive symptoms, the DNA methylation of monozygotic twins that are discordant for adolescent depression and the linkage of DNA methylation to socioeconomic status. In addition, genes in the serotonergic, dopaminergic and brain .derived neurotrophic factor systems have been studied as well as short and long serotonergic allele studies. Some of these have explored both genetic and environmental factors based on genetic/environmental models [58] (Table 6).

Table 6: Genetic markers of adolescent depression.

Heritability	First Author
Dysphoric mood and somatic symptoms moderately heritable	Chen
Low heritability	Sallis
DNA Methylation	
Differences in monozygotic twins discordant on depression	Dempster
Linkage between DNA methylation and risk for adolescent depressionUddin	
Serotonergic, dopaminergic, and brain-derived neurotropic	Xia
Genes	
Short allele and no family support >depression	Li
Long allele and <positive parenting> depression	Little
Brain-derived neurotrophic genes	Xia
Dopaminergic genes	Xia

Heritability

In a study on 613 monozygotic twin pairs and 229 dizygotic pairs, genetic analyses were applied to estimate the Children's Depression Inventory factors that had greater concordance among monozygotic than dizygotic twin pairs [59]. Dysphoric mood, somatic and cognitive symptoms had moderate heritability ranging from 33 to 40%. In contrast, externalizing problems and symptoms of anhedonia had minimal heritability. Although the authors suggested that their findings highlight more environmentally influenced factors, it is not clear why externalizing problems and anhedonia symptoms would be considered more environmentally influenced factors. In much larger samples (3289 to 5480), heritability estimates based on genome-wide complex trait analysis, were low (.07) for adolescents compared to estimates from adults (.21) [60]. For that reason, these authors concluded that environmental factors were more important in the etiology of adolescent than adult depression.

DNA methylation

DNA methylation (the addition of methyl groups to the DNA molecule) can change the activity of a DNA segment without changing the sequence. In a study on adolescent monozygotic twins, 18 pairs of MZ twins were noted to be discordant for

depression (one twin scoring higher than the other) [61]. In this study, DNA methylation was assessed in buccal cell DNA. DNA methylation differences were apparent in MZ twins discordant for adolescent depression, suggesting that DNA methylation may be an underlying mechanism for adolescent depression. In a recent review of the literature, sequential links were noted between low SES, changes in DNA methylation, changes in brain function and risk for depression in adolescent samples [62]. These studies combined highlight the interactive nature of genetic and environmental factors influencing adolescent depression.

Serotonergic, dopaminergic and brain-derived neurotrophic genes

Neurotransmitter systems have also been influenced by genetic factors. In a review of 47 studies, most of the results reflected genetic influences on the serotonergic system (N=26) [63]. Positive associations were noted between depression and serotonergic system genes in 93% of the studies, and 83% of the studies found positive associations between adolescent depression and brain-derived neurotrophic genes. Mixed data have also appeared in this literature on short and long alleles of the serotonin transporter gene. In the National Longitudinal Study of Adolescent Health on 1030 adolescents, for example, less depression occurred in those with the short allele and family support, while greater depression was noted in adolescents with the short allele and no family support suggesting that family support was the differentiating factor [64]. As the authors noted, the short allele may increase reactivity to both negative and positive family influences in the development of depression. In contrast, the long allele of the serotonin transporter gene has been associated with adolescent depression and less positive parenting in two longitudinal samples (N=681 in one sample and N=176 in another sample) [65]. In both of these samples, the long allele of the serotonin transporter gene moderated associations between low levels of positive parenting at early adolescence (11-13 years) and depression in later adolescence (17-19 years). Thus, it would appear that both the short and the long alleles of the serotonin transporter gene have been implicated in the associations between depression and lack of family support. However, the short allele findings derive from cross-sectional data while the long allele results were based on longitudinal samples. And, in the cross-sectional study, associations were noted between the short allele and depression and the lack of support while the longitudinal data suggested the long allele was a moderator of the association between less positive parenting and later depression in adolescents. Although gene modifying interventions have not appeared in this literature, several interventions have focused on modifying parenting and adolescent depression.

INTERVENTIONS

Several types of interventions have been featured in the recent literature on adolescent depression. They include cognitive behavior therapy that has not only been practiced individually but also on the internet and in the classroom. Recently published therapies have also included interpersonal psychotherapy, family therapy, internet therapy, school-based therapy, and lesser known therapies referred to as "Thinking about reward" therapy and "Specifically targeting depression" therapy. Physically-oriented therapies have included transcranial magnetic stimulation therapy and exercise (Table 7).

Table 7: Interventions for adolescent depression.

Intervention	Intervention
Cognitive behavior therapy (CBT)	
Most effective	Weersing, Carnevale
CBT plus fluoxetine effective	Peters
CBT plus antidepressants effective	Rengasany
CBT > effective than bibliotherapy	Rohde
CBT decreased chronic symptoms	Briere
Greater time explaining homework leads to depression	Jungbluth
Texting reminders on homework leads to depression	Kobak
Interpersonal psychotherapy	
Very limited literature	Weersing
Same decrease of depression when compared with group counseling	McCarthy
Family-based therapy	
Parental resistance to accepting diagnosis	Radovic
Parenting strategies	Yap
Behavior exchange systems therapy	Poole [78]
Same results as treatment as usual	Poole [79]

Single session improved parenting	Caramone-Breen
Internet-based interventions	
Motivational interview and brief advice groups <depression	Saulsberry
Motivational interview >brief advice at 2 year follow-up	Richards
School-based interventions	
Education on depression as a treatable medical illness	Ruble
Thinking about reward" best results	Rice
CBT based prevention programs not effective	Taylor
Physical therapies	
Exercise esteemed most important therapy by clinicians	Radovic
Transdermal magnetic stimulation	Lee, Croarkin
Intervention challenges	
Depression stigma decreases treatment-seeking	Dardas [91]
No follow-up care	O'Connor
Not receiving treatment 7x greater odds being depressed at 17 years	Neufeld
Treating comorbid disorders	Curry

Cognitive behavior therapy (CBT)

In the recent literature, cognitive behavior therapy has been the subject of reviews and has been studied both as it is used in the classroom and on the internet. In addition, it has been compared with antidepressants and other forms of therapy like bibliotherapy. Finally, different aspects of the CBT protocol have been assessed including therapist time spent on homework assignments and text message monitoring of homework assignments. An evidence-based review of 42 randomized controlled trials published between 2008 and 2014 suggested that cognitive behavior therapy was the most effective for both child and adolescent depression [66]. This conclusion was qualified by the concern that CBT effects may be less positive in clinically complicated samples and in comparisons between CBT and active control groups. A review of 11 studies suggested that CBT sessions conducted in school settings had also decreased depressive symptomatology in adolescents [67].

Cognitive behavior therapy has frequently been combined with antidepressants for depression, so the relative effectiveness of the pharmacotherapy and psychotherapy is not usually assessed. In a recent study, however, cognitive behavior therapy and fluoxetine effects were separately assessed as well as the combination of the two treatments [68]. In this study on depressed adolescents (N=439), the change score on the Children's Depression Rating Scale from baseline to three

months was used as the outcome measure. The combination treatment was more effective than the separate treatments not only on its average effectiveness but on the number of adolescents who were positively affected. Another research group reported similar results when comparing CBT, fluoxetine and the combination of CBT and fluoxetine in a smaller sample of adolescents (N=196) [69]. Recurrent depression and comorbidities, however, were associated with poorer functioning trajectories and failure to achieve in school and in the workplace, as would be expected. In another study on CBT and antidepressants combined, parent-reported conflict in the clinically significant range predicted less likelihood of remission from depression [70].

Cognitive behavior therapy has been compared with bibliotherapy in at least two studies by the same research group. In the first study, 328 adolescents with depressive symptoms were randomly assigned to a CBT, bibliotherapy or an educational control group [71]. Moderator analyses revealed that the adolescents who had higher baseline depressive symptoms experienced a greater reduction in symptoms in the CBT group versus the bibliotherapy group. In the second study by this group, 631 adolescents were randomly assigned to CBT, bibliotherapy or an educational control group [72]. They identified four trajectories including two positive symptom courses and two negative symptom courses. Surprisingly, more males were in the negative persistent depression trajectory group. CBT preventive interventions did not alter the nature of these trajectories, but they reduced the risk of adolescents following a trajectory of chronically elevated symptoms.

Different CBT techniques have been studied including brief behavior activation, therapists spending more time on homework, adherence to homework and text messaging about homework. In the brief behavior activation study that involved 20 adolescents participating in 8 sessions, 65% required no further psychological intervention [73]. In an observational

study on therapists' homework-related behaviors, audiotapes from the first couple sessions were coded for therapist homework-oriented interaction and those data were used to predict the adolescents' homework-adherence coded from sessions 2 and 3 [74].Greater time spent giving a rationale and explaining homework assignments in session 1 predicted greater adherence at session 2, especially for adolescents who were resistant to homework. Greater time spent on rationale for homework and discussing obstacles to homework in session 2 predicted greater adherence at session 3. In another study on CBT techniques, the CBT intervention consisted of online training of therapists, the use of tablets for teaching the adolescents CBT skills and text messaging for homework reminders and self-monitoring between sessions [75]. Eighteen therapists were randomized to either the CBT or treatment as usual groups for 4 adolescents each for 12 weeks. Knowledge of CBT concepts significantly increased with as many as 95% of the adolescents noting that the texting was helpful. In addition, ratings of the therapeutic alliance were greater in the CBT group. However, the greater decrease in depression for the CBT group was not significant, probably because the statistical power was so low for this small sample size of 36 adolescents per group.

Unfortunately, meta-analyses did not appear in this recent literature on CBT for adolescent depression. This would not only relate to the dearth of CBT studies but also to the highly variable procedures, comparison groups and measures across studies. Nonetheless, its effectiveness across settings and following the use of different techniques informs the literature on evidence-based therapies for adolescent depression.

Interpersonal psychotherapy (IPT)

Fewer studies have been conducted on interpersonal psychotherapy with depressed adolescents. Although a review of 42 randomized control trials suggested that interpersonal psychotherapy was effective in reducing adolescent depression (these results were tempered by the small size of the IPT literature [65]. School-related outcomes including attendance, grades and disciplinary behavior were measured in another interpersonal psychotherapy study [76]. Adolescents were randomly assigned to weekly sessions of IPT or counseling groups. Although the groups did not differ on outcomes, moderation analyses indicated that IPT had more favorable outcomes among more high-risk adolescents (e.g. those from low income families). A decrease in depression was significantly correlated with an improvement in grades. The unexpected equivalence of the two treatment conditions may relate to the counseling sessions being held in groups with the added effect of peer feedback and support. Another possibility is that the one year follow-up assessment session was too remote from the treatment conditions for effects to be noted.

Family-based therapy

Qualitative interviews with primary care providers have revealed the importance of parental social support in the treatment of adolescent depression [77]. In this interview study, the common barriers to adolescent depression treatment were parental resistance to accepting the depression diagnosis and family dysfunction. Parenting strategies for preventing/reducing adolescent depression have been surveyed via Delphi methodology [78] Of 402 recommendations made by parents; an expert panel of 27 international experts endorsed 190 parenting strategies by> 90%. These included don't blame yourself, encourage professional help, encourage your adolescent to deal with anxiety, problems, good health habits and supportive relationships, minimize conflict in the home, establish rules and consequences, be involved and support increasing autonomy, and establish and maintain a good relationship with your adolescent. These have then been used to design treatments such as BEST MOOD [79]. Behavior Exchange Systems Therapy (BEST) is a family systems approach that incorporates psycho education and elements of attachment theories. In one study, eight two-hour multifamily group sessions were delivered over 8 weeks with the parents attending the first four and then the adolescents and siblings joining from week 5. This model was tested in a multi-center, double-blind, randomized controlled trial (N=64 families) by comparing it to a treatment-as-usual supportive parenting program (PAST) [80]. Parents in the BEST MOOD group had significantly lower stress and depression than those in the PAST group. Both groups of adolescents showed a reduction in depressive symptoms which was sustained at a 3-month follow-up. The adolescents may have experienced equivalent peer support in the two types of group interventions thus attenuating the expected greater effects for the BEST MOOD group. And, the parents may have continued

their supportive parenting for the effects to have been sustained for 3 months following the end of the intervention.

A single session online has been effective for improving parenting risk and protective factors [81]. In this study, a community sample of 349 parents and their adolescents were randomly assigned to an online parents' report of their parenting practices and adolescents' report of their depression symptoms. Following individually tailored feedback for the parents' strengths and weaknesses, the parents of the intervention versus the waitlist control group reported improvement, but the adolescents' depression symptoms did not change. The intervention may have impacted the parents' attitudes more than their parenting practices or the parents may have been giving socially desirable responses.

Internet-based interventions

Although the internet has become popular among adolescents such that internet addiction is a major mental health problem in that age group [14], the internet has only appeared as a therapeutic vehicle in two studies by the same group in the recent literature. In a phase II clinical trial, this research group compared two forms of internet therapies including motivational interview versus brief advice [82]. In this randomized clinical trial, both groups showed a decrease in depressed mood, loneliness and self-harm ideation at the one-year follow-up assessment. However, fewer participants in the motivational interviewing group experienced a depressive episode. In a subsequent study by the same research group, the sample (N=44) was followed to 2.5 years [83]. Depression symptoms continued to decrease for the entire cohort. Lower self-efficacy and motivation for depression prevention were related to greater decreases in depression. Although these were randomized trials, they were limited in sample size and in being a pre-post design lacking a treatment as usual control group or a treatment comparison group.

School-based interventions

Most of the school-based interventions for adolescent depression have been educational in nature and most have intended to be preventive. The recent literature also includes studies on the problems of implementing school-based programs. Most of these have been oriented toward psycho education [84] and prevention [85].

In one of the education programs called the Adolescent Depression Awareness Program, high school students were recruited from six schools in Tulsa, Oklahoma (N=710 students) [86]. They were given a school-based education on depression as a treatable medical illness. The students in the intervention group showed a positive change in depression knowledge and attitudes toward help-seeking as measured by the ADAP Depression Knowledge Questionnaire. They also showed an increased willingness to "tell someone" if concerned about depression a peer was experiencing. While these data are promising, this study was not a randomized controlled trial and the questionnaire assessed knowledge and attitudes, not behaviors

In another classroom prevention program, three forms of therapy were compared including a behavioral activation with reward processing therapy called "Thinking about Reward in Young People (TRY), Cognitive Behavior Therapy and Mindfulness Based Cognitive Therapy (MBCT) [87]. The sample was comprised of 256 healthy adolescents age 13-14 with 89% having completed the pre and post assessments. The TRY program which was intended to increase sensitivity to rewarding activities, did increase reward-seeking, and that was related to a decrease in depressive symptoms. The CBT program was associated with reflective negative self-beliefs and the MBCT program with autobiographical memories. These results seemed consistent with the intent of these different forms of therapy. However, this was not a randomized controlled trial because the researchers suggested that randomizing was not feasible. Problems with implementing school-based programs have been identified in a randomized controlled trial across 8 UK secondary schools (N=5030) [88]. In this study that attempted to provide CBT based prevention programs, the trial was not effective. The researchers then tapped the views of the students, teachers and facilitators via interviews that were thematically coded. Although the CBT program was considered to have good content and to be well structured, the challenges of its implementation included the lack of flexibility, the inconsistency of quality, the lack of age appropriateness for all age groups, the demands on teacher time and the failure to prioritize the therapy in the academic setting.

Physical therapies

Surprisingly few studies appear in this literature on physical therapies given that exercise and stimulating the pressure receptors under the skin are noted to increase serotonin, the body's natural antidepressant. This is also surprising given that mental health clinicians endorse exercise as the most important therapy after psychotherapy.

In the only study that could be found on exercise in the recent literature on adolescent depression, mental health clinicians (N=125) were surveyed online on their attitudes and practices regarding exercise prescriptions [89]. The clinicians most frequently ranked exercise as the second most important treatment for depressed adolescents after cognitive behavioral therapy. Exercise was prescribed by the majority of clinicians as "always" (24%) or "most of the time" (43%). Prescription rates were related to clinicians' knowledge regarding exercise but not to their own levels of exercise. For barriers to prescribing exercise, they listed a lack of knowledge about prescribing, a belief that exercise professionals should do the prescribing and the concern that depressed adolescents would not comply with exercise programs. Studies are needed not only on actual prescriptions for exercise but also on adolescent compliance with exercise and effects of the exercise programs.

Transcranial magnetic stimulation is another form of physical therapy. Given that it applies low-intensity continuous current, it is thought to alter cortical excitability [29]. These authors suggest that this therapy can be an important intervention for the delayed or aberrant frontolimbic development in depressed adolescents. In another paper by the same research group, the authors suggest that transcranial magnetic stimulation may modulate imbalances in cortical GABAergic and glutamatergic activity [90]. This form of therapy likely stimulates pressure receptors under the skin which, like massage therapy, would be expected to increase serotonin levels and decrease cortisol levels and depression [15].

Intervention challenges

Several challenges have been noted in this adolescent depression intervention literature. They include the stigma of adolescent depression, parents' unwillingness to accept treatment, adolescents not receiving treatment and those who have not accepted treatment having a seven times greater chance of being depressed at 17 years. Other challenges are the need to improve speed and thoroughness of initial treatment, the need to address comorbid disorders, the lack of follow-up assessments, and preventing relapse and recurrence.

In interviews with 15 primary care providers, as already noted, barriers to treating adolescent depression were discussed and later coded for key themes [76]. The private care providers reported that the unwillingness of parents to accept the adolescents' depression diagnosis was a common barrier along with family dysfunction and trauma. The unwillingness to accept the diagnosis likely relates to the stigma of depression. In a systematic review of studies from Arab countries, 27 studies yielded data suggesting that the depression stigma negatively impacted treatment-seeking among adolescents [91]. In a large sample study from health maintenance organizations in the Western US and a network of community health centers in the Northeast (N=4612), as many as 36% of adolescents who were identified as depressed received no treatment (N=1678) and as many as 19% (N=854) who did receive treatment did not receive follow-up care [92]. Further, 40% of those on antidepressants did not have follow-up care for three months after they started treatment. Those factors that were most predictive of treatment initiation were younger age, more severe symptoms and those receiving a diagnosis of major depression. These data are alarming inasmuch as 14-year-old adolescents who did not receive treatment in another study had seven times greater odds of being depressed by 17 years of age [93] Further challenges for adolescent depression interventions have been noted in a review of that literature [94]. These include improving the speed and thoroughness of the initial treatment response, identifying the successful treatment components, determining how to treat comorbid disorders and preventing relapse and recurrent episodes.

LIMITATIONS AND FUTURE DIRECTIONS

Several limitations can be noted for this recent literature on adolescent depression. First, several seemingly important predictors of depression have not been addressed including, for example, intimacy with friends, intimacy with parents and sleep problems. At least two old studies have addressed these contributions to adolescent depression. In the first of these, adolescents with depressed mood were found to be less intimate with both parents, and they felt less social support and had lower self–esteem than their peers [95] in a second study

by the same group, students with lower depression scores had greater intimacy with both parents [96].

Another limitation of this literature is the focus on single variables even in large sample studies. Although the samples for most of the studies seemed large, the data sets were often focused on only one variable. Multivariate models could be tested by several types of analyses including structural equations, moderating/mediating, profile or multiple regression analyses. The use of several measures and these multivariate analyses might yield more information on predictors of adolescent depression. Studies from an older literature featured multivariate analyses including, for example, research that showed that family relationships, loneliness, depression and substance abuse were related to suicide ideation [97]. Other relationship problems, for example, breakup distress, which is the most frequent problem reported at university counseling centers, has not been addressed in this literature [98]. And, more studies on somatic symptoms that accompany adolescent depression, for example, sleep disturbances would also be informative, especially since they are thought to be influenced by environmental factors and could be responsive to intervention. Another problem is the frequent use of self-reports given that most are taken at school. The students may not report or may be "faking good" to avoid the stigma about adolescent depression. In addition, self–report variables for adolescent depression have not always been measured by psychometrically sound instruments. And some may not be adolescent-oriented as in the frequent use of the adult depression measure (Beck Depression Inventory) or child measure (Children's Depression Inventory).The surveys/questionnaires are often short and simple to ensure student compliance. Further, the direction of effects cannot be determined given that risk factors for depression could be considered effects of depression. For example, depression could lead to sleep disturbances as often as sleep disturbances are a risk factor for depression. The same bidirectionality could be suggested for the relationship between adolescent depression and academic performance. Longitudinal multivariate studies are needed to identify predictors of adolescent depression. Parents, teachers, siblings and peers could be given interviews as well as the adolescents who have been diagnosed as depressed in order to have data from multiple sources. Multivariate studies that include multiple psychometrically sound instruments from multiple informants as well as behavioral and psycho-physiological measures might be more informative. In addition, most of the studies have been cross–sectional versus longitudinal, which has limited any determination of causality. Further, in most of the studies the measures haven't been compared for different levels of depression i.e. depressed mood versus clinically diagnosed depression. Surprisingly, very few intervention studies have appeared in this recent literature. The importance of further intervention research is highlighted by the prevalence and severity of depression in adolescents and the problem that depression can lead to suicidal behavior. In the literature on suicide interventions, school-based and peer-led interventions have been the most effective for preventing suicide ideation and behavior in adolescents. However, in the depressed adolescent intervention literature, school–based interventions were less common and no studies could be found on peer–led interventions. In addition, in many of the studies, interventions have been compared to treatment as usual control groups rather than comparing different types of therapy. Although this literature has a number of limitations, it has highlighted the importance of continuing theoretical and empirical research on adolescent depression as well as interventions to prevent adolescent depression [99-101]. Those might include more Internet–based interventions, more peer–led interventions, more physical interventions, more comparisons between new therapies, more medication versus psychotherapy versus combined interventions and more mixed methods research that involve both quantitative and qualitative methods to more accurately identify adolescents at risk for depression.

REFERENCES

1. Lu W. (2019). Adolescent depression: National trends, risk factors, and healthcare disparities. American Journal of Health and Behavior. 43: 181-194.
2. Dardas LA, Silva SG, Smoski MJ, Noonan D, Simmons, LA. (2018). The prevalence of depressive symptoms among Arab adolescents: Findings from Jordan. Public Health and Nursing. 35: 100-108.
3. Sendi I, Chouikh A, Ammar A, Bouafia N. (2018). Depression in a sample of Tunisian adolescents: Prevalence, associated factors and comorbidity with

anxiety disorders. International Journal of Adolescent Mental Health.

4. Hollenstein T, Allen NB, Sheeber L. (2016). Affective patterns in triadic family interactions: Associations with adolescent depression. Developmental Psychopathology. 28: 85-96.
5. Nelson BW, Byrne ML, Sheeber L, Allen NB. (2017). Does context matter? A multi-method assessment of affect in adolescent depression across multiple affective interaction contexts. Clinical Psychology Science. 5: 239-258.
6. Bodner N, Kuppens P, Allen NB, Sheeber LB, Ceulemans E. (2018). Affective family interactions and their associations with adolescent depression: A dynamic network approach. Dev. Psychopathology. 30: 1459-1473.
7. Mullarkey MC, Marchetti I, Beevers CG. (2018). Using network analysis to identify central symptoms of adolescent depression. Journal of Clinical Child and Adolescent Psychoogy. 13: 1-13.
8. Nardi B, Francesconi G, Catena-Dell'osso M, Bellantuono C. (2013). Adolescent depression: Clinical Features and therapeutic strategies. European Review of Medical Pharmacology and Science.17: 1546-1551.
9. Naicker K, Galambos NL, Zeng Y, Senthilselvan A, Colman I. (2013). Social, Demographic, and health outcomes in the 10 years following adolescent depression. J. Adolescent Health. 52: 533-538.
10. Urrila AS, Paunio T, Palomaki E, Marttunen M. (2015). Sleep in adolescent depression: Physiological perspectives. Acta Physiology. 213: 758-777.
11. Park HY, Heo J, Subramanian SV, Kawachi I, Oh J. (2012). Socioeconomic inequalities in adolescent depression in South Korea: A multilevel analysis. PLoS One. 7:e47025.
12. Respress BN, Morris DL, Gary FA, Lewin LC, Francis SA. (2013). Social Determinants of adolescent depression: An examination of racial differences. Issues in Mental Health Nursing. 34: 539-549.
13. Yang L, Sun L, ZhangZ, Sun Y, Wu H, et al. (2014). Internet addiction, adolescent depression, and the mediating role of life events: Finding from a sample of Chinese adolescents. International Journal of Psychology. 49: 342-347.
14. Clayborne ZM, Varin M, Colman I. (2019). Systematic review and meta-analysis: Adolescent depression and long-term psychosocial outcomes. Journal of the American Academy of Child and Adolescent Psychiatry. 58: 72-79.
15. Field T. (2018). Internet addiction in adolescents: A review. Journal of Addictions and Therapies. 1: 1-11.
16. Field T. (2019). Social touch, CT touch and massage therapy: A narrative review. Developmental Review. 51: 123-145.
17. Marsh HW, Craven RG, Parker PD, Parada RH, Guo J, et al. (2016). Temporal ordering effects of adolescent depression, relational aggression, and victimization over six waves: Fully latent reciprocal effects models. Developmental Psychology. 52: 1994-2009.
18. Davis JP, Dumas TM, Merrin GJ, Espelage DL, Tan K, et al. (2018). Examining the pathways between bully victimization, depression, academic achievement, and problematic drinking in adolescence. Psychology of Addictive Behaviors. 32: 605-616.
19. McLeod GF, Horwood LJ, Fergusson DM. (2016). Adolescent depression, Adult mental health and psychosocial outcomes at 30 and 35 years. Psychology and Medicine. 46: 1401-1412.
20. Rhew IC, Fleming CB, Vander Stoep A, Nicodimos S, Zheng C, et al. (2017). Examination of cumulative effects of early adolescent depression on cannabis and alcohol use disorder in late adolescence in a community-based cohort. Addiction. 112: 1952-1960.
21. Johnson D, Dupuis G, Piche J, Clayborne Z, Colman I. (2018). Adult mental health outcomes of adolescent depression: A systematic review. Depression and Anxiety. 35: 700-716.
22. McGuinness TM, Dyer JG, Wade EH. (2012). Gender differences in adolescent depression. J. Psychosocial Nursing and. Mental Health Services. 50: 17-20.
23. Rawal A, Collishaw S, Thapar A, Rice F. (2013). A direct method of assessing underlying cognitive risk for adolescent depression. Journal of Abnormal Child Psychology. 41: 1279-1288.
24. Orchard F, Reynolds S. (2018). The combined influence of cognitions in adolescent depression: Biases of

interpretation, self-evaluation, and memory. British Journal of Clinical Psychology. 57: 420-435.

25. Auerbach RP, Ho MH, Kim JC. (2014). Identifying cognitive and interpersonal predictors of adolescent depression. Journal of Abnormal Child Psychology. 42: 913-924.
26. Weeks M, Ploubidi GB, Cairney J, Wild TC, Naicker K, et al. (2016). Developmental pathways linking childhood and adolescent depression. Journal of Adolescence. 51: 30-40.
27. Maxwell SD, Fineberg AM, Drabick DA, Murphy SK, Ellman LM. (2018). Maternal prenatal stress and other developmental risk factors for adolescent depression: Spotlight on sex differences. Journal of Abnormal Child Psychology. 46: 381-397.
28. Monti JD, Rudolph KD. (2017). Maternal depression and trajectories of adolescent depression: The role of stress responses in youth risk and resilience. Developmental Psychopathology. 29: 1413-1429.
29. Lee JC, Lewis CP, Daskalakis ZJ, Croarkin PE. (2017). Transcranial direct current stimulation: Considerations for research in adolescent depression. Frontiers of Psychiatry. 8: 91.
30. Gate MA, Watkins ER, Simmons JG, Byrne ML, Schwartz OS, et al. (2013). Maternal parenting behaviors and adolescent depression: The mediating role of rumination. Journal of Clinical Child and Adolescent Psychology. 42: 348-357.
31. Lewis G, Collishaw S, Thapar A, Harold GT. (2014). Parent-child hostility and child and adolescent depression symptoms: The direction of effects, role of genetic factors and gender. European Child and Adolescent Psychiatry. 23: 317-327.
32. Platt B, Cohen Kadosh K, Lau JY. (2013). The role of peer rejection in adolescent depression. Depression and Anxiety. 30: 809-821.
33. Silk JS, Siegle GJ, Lee KH, Nelson EE, Stroud LR, et al. (2014). Increased neural response to peer rejection associated with adolescent depression and pubertal development. Social Cognitive and Affective Neuroscience. 9: 1798-1807.
34. Stikkelbroek Y, Bodden DH, Kleinjan M, Reijnders M, van Baar AL. (2016). Adolescent depression and negative life events, the mediating role of cognitive emotion regulation. PLoS One. 29: 11:e0161062.
35. Nishikawa S, Fujisawa TX, Kojima M, Tomoda A. (2018). Type and timing of negative life events are associated with adolescent depression. Frontiers in Psychiatry. 9: 41
36. Lewis G, Jones PB. , Goodyer IM. (2016). The ROOTS study: A 10-year review of findings on adolescent depression, and recommendations for future longitudinal research. Social Psychiatry and Psychiatric Epidemiology. 51: 161-170.
37. Mestanikova A, Mestanik M, Ondrejka I, Hrtanek I, Cesnekova D, et al. (2019). Complex cardiac vagal regulation to mental and physiological stress in adolescent major depression. Journal of AffectiveDisorder. 249: 234-241.
38. Mestanikova A, Ondrejka I, Mestanik M, Hrtanek I, Snircova E, et al. (2016). Electrodermal activity in adolescent depression. Advances in Experimental Medical Biology. 935: 83-88.
39. Mestanikova A, Ondrejka I, Mestanik M, Cesnekova D, Visnovcova Z, et al. (2017). Pupillary light reflex is altered in adolescent depression. Physiological Research. 66: 277-284.
40. Field T, Diego M. (2008). Maternal Depression Effects on Infant Frontal EEG Asymmetry. International Journal of Neuroscience. 118: 1081-1108.
41. Stewart JG, Mazurka R, Bond L, Wynne-Edwards KE. , Harkness, KL. (2013). Rumination and impaired cortisol recovery following a social stressor in adolescent depression. Journal of Abnormal Child Psychology. 41: 1015-1026.
42. Yaroslavsky, Allard, ES. ,Sanchez-Lopez A. (2019). Can't look away: Attention control deficits predict rumination, depression symptoms and depressive affect in daily life. Journal of Affective Disorders. 245: 1061-1065.
43. Pesce M, Tatangelo R, LaFratta I, Rizzuto A, Campagna G, et al. (2017). Memory training program decreases the circulating level of cortisol and pro-inflammatory cytokines in healthy older adults. Frontiers in Molecular Neuroscience. 10: 233.
44. Pallavi P, Sagar R, Mehta M, Sharma S, Subramanium A, et al. (2015). Serum cytokines and anxiety in adolescent

depression patients: Gender effect. Psychiatry Research. 229: 374-380.

45. Pallavi P, Sagar R, Mehta M, Sharma S, Subramanium A, et al. (2013). Serum neurotrophic factors in adolescent depression: Gender difference and correlation with clinical severity. Journal of Affective Disorders. 150: 415-423.
46. Kovacs M, Yaroslavsky I. (2014). Practitioner review: Dysphoria and its regulation in child and adolescent depression. Journal of Child Psychology and Psychiatry. 55: 741-757.
47. Auerbach RP, Admon R, Pizzagalli DA. (2014). Adolescent depression: Stress and reward dysfunction. Harvard Reviewof Psychiatry. 22: 139-148.
48. Goff B , Tottenham N. (2015). Early-life adversity and adolescent depression: Mechanisms involving the ventral striatum. CNS Spectrum. 20: 337-345.
49. Goff B, Gee DG, Telzer EH, Humphreys KL, Gabard-Durnam L, et al. (2013). Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. Neuroscience. 249: 129-138.
50. Cullen KR, Westlund MK, Klimes-Dougan B, Mueller BA, Houri A, et al. (2014). Abnormal amygdala resting-state functional connectivity in adolescent depression. JAMA Psychiatry. 71: 1138-1147.
51. Connolly CG, Ho TC, Blom EH, LeWinn KZ, Sacchet MD, et al. (2017). Resting-state functional connectivity of the amygdala and longitudinal changes in depression severity in adolescent depression. Journal of Affective Disorders. 207: 86-94.
52. Geng H, Wu F, Kong L, Tang Y, Zhou Q, et al. (2016). Disrupted structural and functional connectivity in prefrontal-hippocampus circuitry in first-episode medication-naïve adolescent depression. PLoS One. 11: e0148345.
53. Henderson SE, Johnson AR, Vallejo AI, Katz L, Wong E, et al, (2013). A preliminary study of white matter in adolescent depression: relationships with illness severity, anhedonia, and irritability. Frontiers in Psychiatry. 4: 152.
54. Ho TC, Wu J, Shin DD, Liu TT, Tapert SF, et al. (2013). Altered cerebral perfusion in executive, affective, and motor networks during adolescent depression. Journal of the American Academy of Child and Adolescent Psychiatry. 52: 1076-1091.
55. Holt RJ, Graham JM, Whitaker KJ, Hagan CC, Ooi C, et al. (2016). Functional MRI of emotional memory in adolescent depression. Developmental and Cognitive Neuroscience. 19: 31-41.
56. Henderson SE, Vallejo AI, Ely BA, Kang G, Krain Roy A, et al. (2014). The neural correlates of emotional face-processing in adolescent depression: A dimensional approach focusing on anhedonia and illness severity. Psychiatry Res. 224: 234-241.
57. Colich NL, Ho TC, Foland-Ross LC, Eggleston C, Ordaz SJ, et al. (2017). Hyperactivation in cognitive control and visual attention brain regions during emotional interference in adolescent depression. Biological Psychiatry. Cognitive Neuroscience and Neuroimaging. 2: 388-395.
58. Gillespie NA, Eaves LJ, Maes H, Silberg JL. (2015). Testing models for the contributions of genes and environment to developmental change in adolescent depression. Behavioral Genetics. 45: 382-393.
59. Chen J, Yu J, Zhang L, Li X, Zhang J. (2014). Etiological heterogeneity of symptom dimensions of adolescent depression. PsyChi Journal. 3: 254-263.
60. Sallis H, Evans J, Wootton R, Krapohl E, Oldehinkel AJ, et al. (2017). Genetics of depressive symptoms in adolescence. BMC Psychiatry. 17: 321.
61. Dempster EL, Wong CC, Lester KJ, Burrage J, Gregory AM, et al. (2014). Genome-wide methylomic analysis of monozygotic twins discordant for adolescent depression. Biological Psychiatry. 76: 977-983.
62. Uddin M, Jansen S , Telzer EH. (2017). Adolescent depression linked to socioeconomic status? Molecular approaches for revealing premorbid risk factors. Bioessays. 39.
63. Xia L, Yao S. (2015). The involvement of genes in adolescent depression: A systematic review. Frontiers in Behavioral Neuroscience. 9: 329.
64. Li JJ, Berk MS, Lee SS. (2013). Differential susceptibility in longitudinal models of gene environment interaction for adolescent depression. Developmental Psychopathology. 25: 991-1003.

65. Little K, Olsson CA, Whittle S, Macdonald JA, Sheeber LB, et al. (2017). Sometimes it's good to be short: The serotonin transporter gene, positive parenting, and adolescent depression. Child Development.
66. Weersing VR, Jeffereys M, Do MT, Schwatrz KT, Bolano C. (2017). Evidence base update of psychosocial treatments for child and adolescent depression. Journal of Clinical Child and Adolescent Psychology. 46: 11-43.
67. Carnevale TD. (2013). Universal adolescent depression prevention programs: A review. The Journal of School Nursing. 29: 181-195.
68. Foster S, Mohler-Kuo M. (2018). Treating a broader range of depressed adolescents with combined therapy. Journal of Affective Disorders. 241: 417-424.
69. Peters AT, Jacobs RH, Feldhaus C, Henry DB, Albano AM, et al. (2016). Trajectories of functioning into emerging adulthood following treatment for adolescent depression. Journal of Adolescent Health. 58: 253-259.
70. Rengasamy M, Mansoor BM, Hilton R, Porta G, He J, et al. (2013). The bi-directional relationship between parent-child conflict and treatment outcome in treatment-resistant adolescent depression. Journal of the American Academy of Child and Adolescent Psychiatry. 52: 370-377.
71. Rohde P, Stice E, Shaw H, Gau, JM. (2015). Effectiveness trial of an indicated cognitive-behavioral group adolescent depression prevention program versus bibiliotherapy and brochure control at 1- and 2-year follow-up. Journal of Consulting and Clinical Psychology. 83: 736-747.
72. Briere FN, Rohde P, Stice E , Morizot J. (2016). Group-based symptom trajectories in indicated prevention of adolescent depression. Depression and Anxiety. 33: 444-451.
73. Pass L, Lejuez CW, Reynolds S. (2018). Brief Behavioural Activation (Brief BA) for adolescent depression: A pilot study. Behavioral Cognitive Psychotherapy. 46: 182-194.
74. Jungbluth NJ, Shirk SR. (2013). Promoting homework adherence in cognitive-behavioral therapy for adolescent depression. Journal of Clinical Child and Adolescent Psychology. 42: 545-553.
75. Kobak KA, Mundt JC, Kennard B. (2015). Integrating technology into cognitive behavior therapy for adolescent depression: A pilot study. Annals of Geneneral Psychiatry. 14: 37.
76. McCarthy AE, Young JF, Benas JS, Gallop RJ. (2018). School-related outcomes from a randomized controlled trial of adolescent depression prevention programs. 26: 170-181
77. Radovic A, Reynolds K, McCauley HL, Sucato GS, Stein BD, et al. (2015). Parents' role in adolescent depression care: Primary care provider perspectives. Journal of Pediatrics. 167: 911-918.
78. Poole LA, Lewis AJ, Toumbourou JW, Knight T, Bertino MD, et al. (2017). A multi-family group intervention for adolescent depression: The BEST MOOD program. Family Processing. 56: 317-330.
79. Poole LA, Knight T, Toumbourou JW, Lubman DI, Bertino MD, et al. (2018). A randomized controlled trial of the impact of a family-based adolescent depression intervention on both youth and parent mental health outcomes. Journal of Abnormal Child Psychology. 46: 169-181.
80. Cardamone-Breen MC, Jorm AF, Lawrence KA, Mackinnon AJ, Yap MBH. (2017). The parenting to reduce adolescent depression and anxiety scale: Assessing parental concordance with parenting guidelines for the prevention of adolescent depression and anxiety disorders. 5: e3825.
81. Saulsberry A, Marko-Holguin M, Blomeke K, Hinkle C, Fogel J, et al. (2013). Randomized clinical trial of a primary care internet-based intervention to prevent adolescent depression: One-year outcomes. Journal of the Canadian Academy of Child and Adolescent Psychiatry. 22: 106-117.
82. Richards K, Marko-Holguin M, Fogel J, Anker L, Ronayne J, et al. (2016). Randomized clinical trial of an internet-based intervention to prevent adolescent depression in a primary care setting(CATCH-IT): 2.5- year outcomes. Journal of Evidence Based Psychotherapy. 16: 113-134.
83. Bevan Jones R, Thapar A, Stone Z, Thapar A, Jones I, et al. (2018). Psychoeducational interventions in adolescent depression: A systematic review. Patient Education Counseling. 101: 804-816.

84. Brown CH, Brincks A, Huang S, Perrino T, Cruden G, et al. (2018). Two-year impact of prevention programs on adolescent depression: An Integrative data analysis approach. Preview Science. 19: 74-94.
85. Ruble AE, Leon PJ, Gilley-Hensley L, Hess SG, Swartz KL, (2013). Depression knowledge in high school students: Effectiveness of the adolescent depression awareness program. Journal of Affective Disorders. 150: 1025-1030.
86. Rice F, Rawal A, Riglin L, Lewis G, Lewis G, et al. (2015). Examining reward-seeking, negative self-beliefs and over-general autobiographical memory mechanisms of change in classroom prevention programs for adolescent depression. Journal of Affective Disorders. 186: 320-327.
87. Taylor JA, Phillips R, Cook E, Georgiou L, Stallard P, et al. (2014). A qualitative process evaluation of classroom-based cognitive behavior therapy to reduce adolescent depression. Internationl Journal ofEnvironmental Research and Public Health. 11: 5951-5969.
88. Radovic S, Melvin GA, Gordon MS. (2018). Clinician perspectives and practices regarding the use of exercise in the treatment of adolescent depression. Journal of Sports Science. 36: 1371-1377.
89. Croarkin PE, MacMaster FP. (2019). Transcranial magnetic stimulation for adolescent depression. Child and Adolescent Psychiatric Clinics of North America. 28: 33-43.
90. Field T. (2019). Suicidal ideation and attempts in adolescents: A narrative view. Submitted for publication.
91. Dardas LA, Bailey DE Jr, Simmons LA. (2016). Adolescent depression in the Arab region: A systematic literature review. Issues in Mental Health Nursing. 37: 569-585.
92. O'Connor BC, Lewandowski RE, Rodriguez S, Tinoco A, Gardner W, et al. (2016). Usual care for adolescent depression from symptom identification through treatment initiation. JAMA Pediatrics. 170: 373-380.
93. Neufeld SAS, Dunn VJ, Jones PB, Croudace TJ, Goodyer IM. (2017). Reduction in adolescent depression after contact with mental health services: A longitudinal cohort study in the UK. Lancet Psychiatry. 4: 120-127.
94. Curry JF. (2014). Future directions in research on psychotherapy for adolescent depression. Journal of Clinical Child and Adolescent Psychology. 43: 510-526.
95. Lasko D, Field T, Gonzalez KP, Harding J, Yando R, et al. (1996). Adolescent depressed mood , parental unhappiness. Adolescence. 31: 49-57.
96. Field T, Lang C, Yando R, Bendell D. (1995). Adolescents' intimacy with parents and friends. Adolescence. 30: 133-140.
97. Jacobs DG, Brewer ML. (2006). Application of the APA practice guidelines on suicide to clinical practice. CNS Spectrums. 11: 447-454.
98. Field T, Diego. M, Pelaez M, Deeds O, Delgado J. (2009). Breakup Distress in University Students. Adolescence. 44: 705-727.
99. Topooco N, Berg M, Johansson S, Liljethorn L, Radvogin E. et al. (2018). Chat- and internet-based cognitive-behavioral therapy in treatment of adolescent depression: Randomised controlled trial. British Journal of Psychiatry. Open. 4: 199-207.
100. Urrila AS, Karlsson L, Kiviruusu O, Pankakoski M, Pelkonen M. et al. (2014). Sleep complaints in adolescent depression: One Year naturalistic follow-up study. BMC Psychiatry. 14: 283.
101. Yap MB, Pilkington PD, Ryan SM, Kelly CM, Jorm AF. (2014). Parenting strategies for reducing the risk of adolescent depression and anxiety disorders: A Delphi consensus study. Journal of Affective Disorders. 156: 67-75.