REVIEW

Depression among adolescents : Clinical features and interventions

Yumiko Izaki

Health Service Office, Health Service, Counseling and Accessibility Center, Tokushima University, Tokushima, Japan

Abstract : Depression often first develops during adolescence, with its rate sharply increasing after puberty and often running a chronic, recurring course thereafter. The development of depression is associated with difficulties in the lives of adolescents and their families, reduced academic achievement, suicide, and increased socio-economic disadvantage in adulthood. Earlier and more effective interventions for depression in adolescents are required. This review describes the updated etiology and clinical features of adolescent depression, and focuses on appropriate therapeutic strategies to adopt in clinical practice. J. Med. Invest. 68 : 22-28, February, 2021

INTRODUCTION

Depression is a syndrome composed of multiple symptoms, such as depressed mood and loss of interest, and depression in childhood and adolescence is diagnosed from clinical symptoms using the same diagnostic criteria as adult depression (1). The prevalence of depression in childhood is 1-2% with no gender difference, and it increases sharply in adolescence. A recent epidemiological study reported the 12-month prevalence of depressive disorder in adolescents to be 8.2%, being approximately two-fold higher in girls than in boys (2). The onset of depression peaks between the ages of 15 and 18, with the highest gender ratio (3). Adolescent onset depression is more heritable than preadolescent onset depression, and more chronic and recurrent than adult onset depression (4). In addition, there are important differences between adolescent and adult depression in terms of treatment response. Rapid biological and social development during adolescence is hypothesized to induce depression in those who are vulnerable. This review describes the updated etiology and clinical features, and focuses on appropriate therapeutic interventions for adolescent depression. In this article, depression is synonymous with major depressive disorder (MDD).

VULNERABILITY TO DEPRESSION AMONG ADOLESCENTS

Heredity

Family studies and twin studies revealed that offspring with depressed parents had a two- to four-fold increase in the risk of depression (5-7). However, the proportion of genetic factors in the development of depression is 30~40%, lower than that of schizophrenia and bipolar disorder (8). Depression is caused by the interaction of genetic and environmental factors. Serotonin-transporter-linked polymorphic region (5-HTTLPR) is the most frequently reported candidate gene associated with early-onset depression. Individuals with the short 5-HTTLPR

variant exhibited more diagnosable depression in relation to a history of child abuse and later stressful life event, whereas individuals without the short 5-HTTLPR variant had no change in the risk of developing depression despite having similar experiences (9, 10). These studies emphasized the effects of 5-HTTLPR and stress interaction (GxE interaction) on the development of depression. There are also many reports of a positive association between methylation of brain-derived neurotropic factor (BDNF) gene, one of the epigenetic decorations on the genome caused by environmental factors, and adolescent depression (11).

Environmental risk factors
Child maltreatment and family adversity

Childhood abuse and family dysfunction increased the risk of developing depression in children, and experiences of abuse and family dysfunction in adolescence also increased the risk of developing depression (12). In addition, childhood abuse increased the onset of depression from adolescence to adulthood, earlier than controls, and most first-time episodes appeared between the ages of 12 and 15 (13, 14).

A study that investigated the relationship between family-focused adverse experiences from early childhood to adolescence and adolescent mental health reported that both the moderate adversity group (family loss/discord, economic difficulties, maternal mental illness, and father's atypical parenting) and severe adversity group (including child abuse) increased the risk of developing disruptive behavior disorders and depression, respectively, compared with the low adversity group. In the severe adversity group, the odds rate was associated with an 8.0-fold increase in disruptive behavior disorders and 4.8-fold increase in depression (15).

Peer victimization

Peer victimization in childhood increased the risk of developing depression and anxiety in early adolescence, and depressive symptoms were more likely to be prolonged (16). The experience of bullying in childhood also increased the risk of developing depression and suicidality even in mid-adolescence (17). In both studies, individuals victimized by peers had a greater risk of reporting depression even after adjustment for family adversity, and more serious bullying had a greater impact.

Pubertal endocrine alterations

Exposure to sex hormones in the brain during puberty

activates the development and coordination of the prefrontal cortex, amygdala, and hypothalamus. Hormonal and physical changes accompanying puberty may be associated with an increased risk of depression in puberty ; however, the mechanism is unknown. A linear relationship between estrogen levels and depressive symptoms in pre- and post-pubertal girls was previously reported, and a weak association between estrogen levels and negative affect was identified (14, 18). Furthermore, increased levels of oxytocin may increase the desire for interpersonal connection among adolescent girls, which is likely to cause hypersensitivity to interpersonal breakups and conflict, thereby increasing their vulnerably to developing depression (18-20).

NEUROBIOLOGY

Neurotransmission and endocrinology
Serotonin and dopamine systems

The serotonin (5-HT) system starts developing before birth and matures in early childhood. As serotonin regulates neuroplasticity, dysfunction of 5-HT system and serotonergic neuroplasticity, especially during early life, may be related to the pathophysiology of depression (21). On the other hand, the dopamine system matures during adolescence. Exposure to stress during this period can affect maturation of the frontal cortex, inducing impulse dysregulation and neuropsychiatric disorders (22).

Hypothalamus–pituitary–adrenal axis

Hypercortisolemia and non-suppression on the dexamethasone suppression test (DST) are noted in depressed adults (23, 24). The hypothalamus–pituitary–adrenal (HPA) axis, the major stress system in the body, is a neuroendocrine system involved in the production of the stress hormone cortisol by the adrenal glands. However, neurotoxicity and neuroinflammation by excessive exposure of the hippocampus to glucocorticoids cause glucocorticoid-induced changes in synaptic plasticity, reduction in neurogenesis, and in some cases, neuronal atrophy and cell death. Prenatal and childhood adversity can lead to a decreased hippocampal volume and long-term dysregulation of the HPA axis, resulting in diminished memory and learning abilities and increased risk of developing future depression (25-27). HPA-axis dysregulation, such as high baseline cortisol levels and atypical responses to DST, has also been observed in children and adolescents with depression (28). Adolescents with depression who have higher cortisol levels required a longer time to recover from depressive episodes and were more likely to exhibit recurrence after stressful experiences (29).

Sleep

Insomnia has a bidirectional relationship with the onset and growth of depressive symptoms. In relation to circadian rhythms, adolescent depression predicted the eveningness chronotype, whereas the eveningness chronotype predicted depressive symptoms and the onset of depression, which suggests an interaction between depression and chronotype in adolescents (30).

Neurophysiology
Emotional regulation

Positive affectivity/affect (PA) increases gradually in children of normal control parents. In contrast to the normative increase in PA, negative affectivity/affect (NA) displays generally decrease from infancy up to around late childhood. However, in a longitudinal study of offspring with and without a high familial risk for depression from 1 to 9 years of age, there was no difference in NA, but PA was consistently low in high-risk children (31). In a study of face processing in children and adolescents at high risk and low risk using fMRI, high-risk subjects exhibited higher activity in the amygdala and nucleus accumbens (a part of the striatum) for scary facial expressions, and lower activity for happy facial expressions (32). A study that examined attentional bias to emotional faces (sad, angry, and happy compared with neutral) found that depressed adolescents demonstrated a selective attention bias towards sad faces compared with controls among past and current MDD patients. In addition, adolescents with both depression and anxiety had an attention bias to both sad and angry faces, with boys avoiding happy faces (33). In an affective go/no go task, only adolescents with current MDD responded more quickly to negative (sad) words, had delayed responses to positive (happy) words, and had a selective attention bias to negative words and poor attention switching compared with healthy subjects and MDD patients in remission (34).

Low PA and attention to negative emotional stimuli in children and adolescents at high risk of depression are considered to be the core factors for developing depression (35).

Reward processing and decision making

The approach system is related to reward behaviors and is largely controlled by the ventral striatum. The avoidance system is related to avoidance behaviors and is mostly controlled by the amygdala. The ability of cognitive control to suppress inappropriate behaviors in favor of goal-oriented ones generally increases linearly from childhood to adolescence. Adolescents exhibit similar activity in the ventral striatum to adults, but the activity in their prefrontal regions is more similar to that in children. Thus, during adolescence relative to childhood or adulthood, immature prefrontal region engagement may not provide sufficient top-down control via the activated ventral striatum, which may explain why adolescents are more likely to engage in risky or reward-dependent behaviors compared with children and adults (36). The development of both reward function and executive function is likely based on changes in dopamine function (37). However, in situations where emotive cues are not present, cortical control systems are not impaired, leading adolescents to more optimal behaviors (36). Therefore, in adolescents, adaptive and goal-oriented behaviors require the maturation of systems to process emotional stimuli, reward functions, and cognitive control.

Adolescence may be the developmental period during which reward function in depression is most markedly disrupted. Adolescents with depression exhibit reduced reactivity in the striatum in response to decision making, anticipation, and outcomes involving monetary rewards. However, the medial prefrontal cortex (mFC) responses were not consistent with higher or lower outcomes (38). Interventions related to mindfulness can reduce mFC over-regulation if the reward function is impaired through over-regulation of the mFC striatum. If the reward function is impaired due to an initially low striatum reaction to the reward, the initial striatum reaction may be increased through pharmacological means (38).

RESILIENCE

Warm supportive relationships, more adaptive emotional regulation skills, and an adaptive coping style for stress can protect at-risk adolescents from developing depression (39-42). Among resilient adolescent girls, individuals with a familial risk of depression who did not develop depression had greater connectivity between the amygdala and orbitofrontal cortex than

high-risk individuals who developed depression. In the resilient girls group only, the strength of amygdala-orbitofrontal cortex connectivity was correlated with positive life events. Resilient adolescent females had compensatory functional connectivity patterns in emotional regulatory networks that correlated with positive life events, suggesting that experience-dependent plasticity within these networks confers resilience to depression (41). Adolescents with a history of childhood maltreatment who were better able to regulate emotions through regulating amygdala reactivity by the prefrontal region had a lower risk of depression over time (42).

CLINICAL FEATURES

Symptoms

The clinical symptoms of MDD in children and adolescents have similarities with those in adults, but there are several differences that can be attributed to the physical, emotional, cognitive, and social developmental stages of children and adolescents. DSM-5 criteria describe in the note that depressed mood can be irritable mood in children and adolescents, and that body weight loss consider failure to make expected weight gain in children.

In both children and adolescents, vegetative symptoms (appetite and weight change, insomnia, and fatigue) are common and physical complaints, such as headaches and abdominal pain, are more likely to be observed in children and adolescents than in adults (43, 44). A previous meta-analysis reported that the baseline rates of suicide-related symptoms (suicidal thoughts and behaviors) in adolescents, adults, and geriatric patients enrolled in randomized controlled trials (RCT) of pharmacotherapy for depression were 20%, 5%, and 3%, respectively (45).

Cole *et al*. conducted a large multi-site trial to evaluate more reliable data about depression severity than conventional symptom counts in 5- to 18-year-old child and adolescent depression by using item response theory (IRT). According to their study, concentration problems, worthlessness/guilt, and sleep disturbance were noted at mild depression, whereas psychomotor agitation/retardation, appetite/weight disturbance, and suicidal ideation/attempts were noted at severer levels of depression (46).

Comparing the symptoms that pediatric and adolescent depression patients had in common, anhedonia, weight change, hypersomnia, serious suicide attempts, and use of alcohol and illicit drugs were more common in adolescents. There were no sex differences other than female adolescents having greater suicidality (47, 48).

Thus, in adolescent depression, depressed mood, irritability, and anhedonia are the core symptoms, followed by physical symptoms of appetite and weight change, insomnia, and hypersomnia, with suicidal ideation and attempts more likely observed in severe cases.

Bipolar depression

Diagnosis of Bipolar disorder (BP) requires the presence of at least one past manic or hypomanic episode, but the first episode of BP in youth is usually a depressive episode. The risk of BP in prepubertal depression is estimated to be 10-20% (49). It takes an average of 10 years to correctly identify and begin the treatment of BP, therefore more useful index for differential diagnosis in clinical symptoms between unipolar and bipolar depression is needed. Clinical features that predict bipolar depression include family history of bipolar disorder, as well as depression with psychotic features, hypomania associated with antidepressant use, depression with mixed features and with subsyndromal manic symptoms, particularly motor hyperactivity, distractibility, and pressured speech (49-52).

Prodromal symptoms

Insomnia is a well-known precursor to depression in adults, and even in children, a twin study reported that insomnia at age 8 predicted depression at age 10 (53). Subthreshold depressive symptoms increase the risk of MDD after one year (54, 55). Anxiety symptoms often precede depression, but twin studies also suggested genetic effects (56, 57).

Comorbidity

Adolescents with depression often have other psychiatric disorders (6, 58). Anxiety disorders are most often comorbid with depression or precede depression (59-61). Attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and substance abuse are also common comorbidities. In particular, ADHD is more common with pediatric depression and substance abuse is more common with adolescent depression (48).

TREATMENTS FOR ADOLESCENT DEPRESSION

Treatment of depression is divided into three phases : acute treatment for 2-3 months, consolidation therapy for 3-6 months, and maintenance therapy for 12 months or longer. For all patients, consolidation therapy is required to prevent recurrence, and maintenance therapy is performed for more severe, recurrent, and chronic patients. Each phase of treatment should include psychoeducation, supportive psychotherapy or management, family involvement, and school involvement. In uncomplicated or briefly depressed adolescents, or those with mild psychosocial impairment, these basic interventions alone can have therapeutic effects. In adolescents with moderate to severe depression, chronic and recurrent depression, or suicidality, interventions using more specific types of treatments, such as cognitive behavioral therapy (CBT), interpersonal therapy (IPT), pharmacotherapy, or a combination of pharmacotherapy and psychotherapy, are required. Adolescents with moderate depression can only be treated by CBT or IPT, but more severe depression generally requires medication (62).

CBT

CBT focuses on identifying cognitive distortions that may lead to depressive mood using problem-solving techniques and behavioral activation methods, and emotional regulation skills and other skills to control and overcome depression. There is weaker evidence for CBT (and IPT) in the treatment of children with depression even though it is a well-established intervention for adolescents with depression (63, 64). The Treatment of Adolescent Depression Study (TADS) was a large multi-center RCT that examined the effectiveness of standard treatment options for MDD in adolescents, and compared the therapeutic effects in four groups : CBT-only, fluoxetine only, CBT and fluoxetine, and placebo group. Although CBT-only treatment was not more effective than placebo, the combination of CBT and pharmacotherapy (fluoxetine) in the treatment of adolescents with moderate to severe depression was the most effective (65, 66). However, CBT is less effective in adolescents with a history of abuse or trauma, current parental depression, or low income (63). In the analysis of Treatment of SSRI-Resistant Depression in Adolescents (TORDIA), combined treatment with CBT and antidepressants was more advantageous for adolescents whose depression was more severe (67). Providing personalized treatment components for adolescents with multiple problems, such as behavioral problems, in addition to depression and interventions integrated with trauma-focused CBT is useful for abused depressed adolescents

(68, 69).

IPT

IPT conceptualizes depression in relation to loss, role conflict, and inconsistencies in personal relationships. Therefore, IPT aims to help individuals with depression reduce their personal conflicts by teaching problem-solving skills in human relationships, and helping to correct dysfunctional communication and relationship patterns. IPT was demonstrated to be superior to supportive management twice a month, with the most marked difference in late adolescents with moderate or severe depression (70). IPT was as effective as CBT against adolescent depression (71).

Pharmacotherapy

Tricyclic antidepressants, which are effective for adult depression, are not effective for childhood depression and less effective for adolescent depression (72). Adolescents receiving a serotonin re-uptake inhibitor (SSRI) had a good response rate of approximately 60%, but the response rate was 35% to 60% for placebo (65, 73-75). These small or no differences between the SSRI and placebo were considered to be in part because depressive symptoms in youth can respond better to supportive management, and that these studies included subjects with mild to moderate depression or those with low antidepressant doses and other methodological problems (62, 75). Studies that enrolled more severe participants had lower placebo response rates, and reported significant differences between drugs and placebos (76). Antidepressants demonstrated to be effective compared with placebo were fluoxetine, sertraline, citalopram/escitalopram, and venlafaxine, but their effects on depression and anxiety were higher in adolescents than in children, and only fluoxetine was effective for childhood depression in patients under 12 years of age compared with placebo (77).

A meta-analysis of 24 previous RCT of 9 different antidepressants by the FDA reported that antidepressants slightly increased suicidal ideation, which led to placement of the 'Black Box Warning' on all classes of antidepressants in children and adolescents. However, in a subsequent thorough meta-analysis, the overall number needed to harm (NNT to observe one adverse event caused by active treatment) for MDD was 112. The overall NNT of antidepressants for childhood depression is 10. Therefore, considering the limitations of meta-analyses, nearly 11-times more depressed patients may respond favorably to antidepressants than spontaneously report suicidality (62, 77).

However, suicide ideation and behaviors in adolescent depression were reported to decrease with the improvement of depressive symptoms by antidepressants, as in adults and geriatric patients, but the significant reduction in suicidal thoughts and behaviors due to antidepressants observed in adults and geriatric patients was not observed in adolescents (45). Therapeutic options other than medication are thus required, especially for suicidal ideation and behaviors in children and adolescents.

PREVENTION

CBT- and IPT-based interventions as prevention programs have been developed as preventive interventions for children and adolescents with depression. The purpose of these preventive interventions is to prevent depression or delay the onset of clinically significant symptoms. Implementing preventive programs for children when their behavior is more amenable is more likely to produce better outcomes than if treatment is administered after rigid patterns of cognition and behavior have been established (78). A systematic review of school-based prevention programs for children aged 5 to 19 reported small preventive effects (effect sizes d = 0.12 to 0.23) against depression after intervention and follow-up at 6 and 12 months. In the subgroup analysis, targeted populations were more effective than universal populations, and programs for children were more effective than programs for late adolescents (78). Based on Cochrane's review of meta-analyses in clinical and community-settings, and school-based trials, the trials were effective for depressive symptoms up to 12 months, had no long-term effects, and were significantly more effective at targeted prevention (79). A RCT of a cognitive-behavioral prevention program for high-risk adolescents with parental depression reduced the rate of depression after 6 years (80). Kovacs noted that preventive trials for youth MDD may benefit from a combined approach of new or different interventions based on case selection that combines multiple indicators of vulnerability (35).

CONCLUSIONS

In therapeutic interventions for adolescent depression, it is important to consider the biological and environmental vulnerabilities of individuals, and to assess their emotional, cognitive, and behavioral characteristics. Evaluating the severity of depression and comorbid symptoms is also required to optimize treatment. A targeted approach in early childhood may be effective at preventing the development of depression.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

REFERENCES

1. American Psychiatric Association : Diagnostic and Statistical Manual of Mental Disorders 5th edn. American Psychiatric Association, Washington, DC, 2013
2. Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JG, Gruber MJ, He JP, Koretz D, McLaughlin KA, Petukhova M, Sampson NA, Zaslavsky AM, Merikangas KR : Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. Archives of general psychiatry 69 : 372-380, 2012
3. Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE : Development of depression from preadolescence to young adulthood : emerging gender differences in a 10-year longitudinal study. J Abnorm Psychol 107 : 128-140, 1998
4. Zisook S, Rush AJ, Lesser I, Wisniewski SR, Trivedi M, Husain MM, Husain MM, Balasubramani GK, Alpert JE, Fava M : Preadult onset vs. adult onset of major depressive disorder : a replication study. Acta Psychiatr Scand 115 : 196-205, 2007
5. Rice F, Harold GT, Thapar A : The Link between depression in mothers and offspring : an extended twin analysis. Behav Genet 35 : 565-577, 2005
6. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Verdeli H, Pilowsky DJ, Grillon C, Bruder G : Families at high and low risk for depression : a 3-generation study. Archives of general psychiatry 62 : 29-36, 2005
7. Pilowsky DJ, Wickramaratne P, Nomura Y, Weissman MM : Family discord, parental depression, and psychopathology in offspring : 20-year follow-up. J Am Acad Child Adolesc Psychiatry 45 : 452-460, 2006

8. Sullivan PF, Neale MC, Kendler KS : Genetic epidemiology of major depression : review and meta-analysis. The American journal of psychiatry 157 : 1552-1562, 2000

9. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R : Influence of life stress on depression : moderation by a polymorphism in the 5-HTT gene. Science 301 : 386-389, 2003

10. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE : Genetic sensitivity to the environment : the case of the serotonin transporter gene and its implications for studying complex diseases and traits. The American journal of psychiatry 167 : 509-527, 2010

11. Xia L, Yao S : The Involvement of Genes in Adolescent Depression : A Systematic Review. Front Behav Neurosci 9 : 329, 2015

12. Shanahan L, Copeland WE, Costello EJ, Angold A : Child-, adolescent- and young adult-onset depressions : differential risk factors in development? Psychol Med 41 : 2265-2274, 2011

13. Widom CS, DuMont K, Czaja SJ : A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Archives of general psychiatry 64 : 49-56, 2007

14. Andersen SL, Teicher MH : Stress, sensitive periods and maturational events in adolescent depression. Trends Neurosci 31 : 183-191, 2008

15. Dunn VJ, Abbott RA, Croudace TJ, Wilkinson P, Jones PB, Herbert J, Goodyer IM : Profiles of family-focused adverse experiences through childhood and early adolescence : the ROOTS project a community investigation of adolescent mental health. BMC Psychiatry 11 : 109, 2011

16. Zwierzynska K, Wolke D, Lereya TS : Peer victimization in childhood and internalizing problems in adolescence : a prospective longitudinal study. J Abnorm Child Psychol 41 : 309-323, 2013

17. Geoffroy MC, Boivin M, Arseneault L, Renaud J, Perret LC, Turecki G, Michel G, Salla J, Vitaro F, Brendgen M, Tremblay RE, Côté SM : Childhood trajectories of peer victimization and prediction of mental health outcomes in midadolescence : a longitudinal population-based study. CMAJ 190 : 37-43, 2018

18. Reinecke MA, Simmons A : Vulnerability to depression among adolescents : Implications for cognitive-behavioral treatment. Cogn Behav Pract 12 : 166-176, 2005

19. Cyranowski JM, Frank E, Young E, Shear MK : Adolescent onset of the gender difference in lifetime rates of major depression : a theoretical model. Archives of general psychiatry 57 : 21-27, 2000

20. Monroe SM, Rohde P, Seeley JR, Lewinsohn PM : Life events and depression in adolescence : relationship loss as a prospective risk factor for first onset of major depressive disorder. J Abnorm Psychol 108 : 606-614, 1999

21. Kraus C, Castrén E, Kasper S, Lanzenberger R : Serotonin and neuroplasticity - Links between molecular, functional and structural pathophysiology in depression. Neurosci Biobehav Rev 77 : 317-326, 2017

22. Suri D, Teixeira CM, Cagliostro MK, Mahadevia D, Ansorge MS : Monoamine-sensitive developmental periods impacting adult emotional and cognitive behaviors. Neuropsychopharmacology 40 : 88-112, 2015

23. Paslakis G, Krumm B, Gilles M, Schweiger U, Heuser I, Richter I, Deuschle M : Discrimination between patients with melancholic depression and healthy controls : comparison between 24-h cortisol profiles, the DST and the Dex/CRH test. Psychoneuroendocrinology 36 : 691-698, 2011

24. Christensen MV, Kessing LV : The hypothalamo-pituitary-adrenal axis in major affective disorder : a review. Nord J Psychiatry 55 : 359-363, 2001

25. Frodl T, O'Keane V : How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiol Dis 52 : 24-37, 2013

26. Wilkinson PO, Goodyer IM : Childhood adversity and allostatic overload of the hypothalamic-pituitary-adrenal axis : a vulnerability model for depressive disorders. Dev Psychopathol 23 : 1017-1037, 2011

27. Rao U, Chen LA, Bidesi AS, Shad MU, Thomas MA, Hammen CL : Hippocampal changes associated with early-life adversity and vulnerability to depression. Biological psychiatry 67 : 357-364, 2010

28. Lopez-Duran NL, Kovacs M, George CJ : Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents : a meta-analysis. Psychoneuroendocrinology 34 : 1272-1283, 2009

29. Rao U, Hammen CL, Poland RE : Longitudinal course of adolescent depression : neuroendocrine and psychosocial predictors. J Am Acad Child Adolesc Psychiatry 49 : 141-151, 2010

30. Haraden DA, Mullin BC, Hankin BL : The relationship between depression and chronotype : A longitudinal assessment during childhood and adolescence. Depress Anxiety 34 : 967-976, 2017

31. Olino TM, Lopez-Duran NL, Kovacs M, George CJ, Gentzler AL, Shaw DS : Developmental trajectories of positive and negative affect in children at high and low familial risk for depressive disorder. J Child Psychol Psychiatry 52 : 792-799, 2011

32. Monk CS, Klein RG, Telzer EH, Schroth EA, Mannuzza S, Moulton JL, Guardino M, Masten CL, McClure-Tone EB, Fromm S, Blair RJ, Pine DS, Ernst M : Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. The American journal of psychiatry 165 : 90-98,2008

33. Hankin BL, Gibb BE, Abela JR, Flory K : Selective attention to affective stimuli and clinical depression among youths : role of anxiety and specificity of emotion. J Abnorm Psychol 119 : 491-501, 2010

34. Maalouf FT, Clark L, Tavitian L, Sahakian BJ, Brent D, Phillips ML : Bias to negative emotions : a depression state-dependent marker in adolescent major depressive disorder. Psychiatry Res 198 : 28-33, 2012

35. Kovacs M, Lopez-Duran N : Prodromal symptoms and atypical affectivity as predictors of major depression in juveniles : implications for prevention. J Child Psychol Psychiatry 51 : 472-96, 2010

36. Casey B, Jones RM, Somerville LH : Braking and Accelerating of the Adolescent Brain. J Res Adolesc 21 : 21-33, 2012

37. Davey CG, Yücel M, Allen NB : The emergence of depression in adolescence : development of the prefrontal cortex and the representation of reward. Neurosci Biobehav Rev 32 : 1-19, 2008

38. Forbes EE, Dahl RE : Research Review : altered reward function in adolescent depression : what, when and how? J Child Psychol Psychiatry 53 : 3-15, 2012

39. Gariépy G, Honkaniemi H, Quesnel-Vallée A : Social support and protection from depression : systematic review of current findings in Western countries. Br J Psychiatry 209 : 284-293, 2016

40. Wetter EK, Hankin BL : Mediational pathways through which positive and negative emotionality contribute to

anhedonic symptoms of depression : a prospective study of adolescents. J Abnorm Child Psychol 37 : 507-520, 2009

41. Fischer AS, Camacho MC, Ho TC, Whitfield-Gabrieli S, Gotlib IH : Neural Markers of Resilience in Adolescent Females at Familial Risk for Major Depressive Disorder. JAMA psychiatry 75 : 493-502, 2018

42. Rodman AM, Jenness JL, Weissman DG, Pine DS, McLaughlin KA : Neurobiological Markers of Resilience to Depression Following Childhood Maltreatment : The Role of Neural Circuits Supporting the Cognitive Control of Emotion. Biological psychiatry 86 : 464-473, 2019

43. Rice F, Riglin L, Lomax T, Souter E, Potter R, Smith DJ, Thapar AK, Thapar A : Adolescent and adult differences in major depression symptom profiles. Journal of affective disorders 243 : 175-181, 2019

44. Nardi B, Francesconi G, Catena-Dell'osso M, Bellantuono C : Adolescent depression : clinical features and therapeutic strategies. Eur Rev Med Pharmacol Sci 17 : 1546-1551, 2013

45. Gibbons RD, Brown CH, Hur K, Davis J, Mann JJ : Suicidal thoughts and behavior with antidepressant treatment : re-analysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Archives of general psychiatry 69 : 580-587, 2012

46. Cole DA, Cai L, Martin NC, Findling RL, Youngstrom EA, Garber J, Curry JF, Hyde JS, Essex MJ, Compas BE, Goodyer IM, Rohde P, Stark KD, Slattery MJ, Forehand R : Structure and measurement of depression in youths : applying item response theory to clinical data. Psychol Assess 23 : 819-833, 2011

47. Ryan ND, Puig-Antich J, Ambrosini P, Rabinovich H, Robinson D, Nelson B, Iyengar S, Twomey J : The clinical picture of major depression in children and adolescents. Archives of general psychiatry 44 : 854-861, 1987

48. Yorbik O, Birmaher B, Axelson D, Williamson DE, Ryan ND : Clinical characteristics of depressive symptoms in children and adolescents with major depressive disorder. J Clin Psychiatry 65 : 1654-1659, 2004

49. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL : Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. The American journal of psychiatry 158 : 125-127, 2001

50. Strober M, Carlson G : Bipolar illness in adolescents with major depression : clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Archives of general psychiatry 39 : 549-555, 1982

51. Uchida M, Serra G, Zayas L, Kenworthy T, Faraone SV, Biederman J : Can unipolar and bipolar pediatric major depression be differentiated from each other? A systematic review of cross-sectional studies examining differences in unipolar and bipolar depression. Journal of affective disorders 176 : 1-7, 2015

52. Diler RS, Goldstein TR, Hafeman D, Merranko J, Liao F, Goldstein BI, Hower H, Gill MK, Hunt J, Yen S, Keller MB, Axelson D, Strober M, Iyengar S, Ryan ND, Birmaher B : Distinguishing Bipolar Depression from Unipolar Depression in Youth : Preliminary Findings. Journal of child and adolescent psychopharmacology 27 : 310-319, 2017

53. Gregory AM, Rijsdijk FV, Lau JY, Dahl RE, Eley TC : The direction of longitudinal associations between sleep problems and depression symptoms : a study of twins aged 8 and 10 years. Sleep 32 : 189-99, 2009

54. Georgiades K, Lewinsohn PM, Monroe SM, Seeley JR : Major depressive disorder in adolescence : the role of subthreshold symptoms. J Am Acad Child Adolesc Psychiatry 45 : 936-944, 2006

55. Klein DN, Shankman SA, Lewinsohn PM, Seeley JR : Subthreshold depressive disorder in adolescents : predictors of escalation to full-syndrome depressive disorders. J Am Acad Child Adolesc Psychiatry 48 : 703-710, 2009

56. Rice F, van den Bree MB, Thapar A : A population-based study of anxiety as a precursor for depression in childhood and adolescence. BMC Psychiatry 4 : 43,2004

57. Middeldorp CM, Cath DC, Van Dyck R, Boomsma DI : The co-morbidity of anxiety and depression in the perspective of genetic epidemiology. A review of twin and family studies. Psychol Med 35 : 611-624, 2005

58. Angold A, Costello EJ, Erkanli A : Comorbidity. J Child Psychol Psychiatry 40 : 57-87, 1999

59. Chaplin TM, Gillham JE, Seligman ME : Gender, Anxiety, and Depressive Symptoms : A Longitudinal Study of Early Adolescents. J Early Adolesc 29 : 307-327, 2009

60. Keenan K, Feng X, Hipwell A, Klostermann S : Depression begets depression : comparing the predictive utility of depression and anxiety symptoms to later depression. J Child Psychol Psychiatry 50 : 1167-1175, 2009

61. Brady EU, Kendall PC : Comorbidity of anxiety and depression in children and adolescents. Psychol Bull 111 : 244-255, 1992

62. Birmaher B, Brent D, Bernet W, Bukstein O, Walter H, Benson RS, Chrisman A, Farchione T, Greenhill L, Hamilton J, Keable H, Kinlan J, Schoettle U, Stock S, Ptakowski KK, Medicus J : Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 46 : 1503-1526, 2007

63. Weersing VR, Jeffreys M, Do MT, Schwartz KT, Bolano C : Evidence Base Update of Psychosocial Treatments for Child and Adolescent Depression. J Clin Child Adolesc Psychol 46 : 11-43, 2017

64. Forti-Buratti MA, Saikia R, Wilkinson EL, Ramchandani PG : Psychological treatments for depression in pre-adolescent children (12 years and younger) : systematic review and meta-analysis of randomised controlled trials. Eur Child Adolesc Psychiatry 25 : 1045-1054, 2016

65. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J : Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression : Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 292 : 807-820, 2004

66. March JS, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J : The Treatment for Adolescents With Depression Study (TADS) : long-term effectiveness and safety outcomes. Archives of general psychiatry 64 : 1132-1143, 2007

67. Asarnow JR, Emslie G, Clarke G, Wagner KD, Spirito A, Vitiello B, Iyengar S, Shamseddeen W, Ritz L, McCracken J, Strober M, Suddath R, Leonard H, Porta G, Keller M, Brent D : Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents : predictors and moderators of treatment response. J Am Acad Child Adolesc Psychiatry 48 : 330-339, 2009

68. Weisz JR, Chorpita BF, Palinkas LA, Schoenwald SK, Miranda J, Bearman SK, Daleiden EL, Ugueto AM, Ho A, Martin J, Gray J, Alleyne A, Langer DA, Southam-Gerow MA, Gibbons RD : Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth : a randomized effectiveness trial. Archives of general psychiatry 69 : 274-282, 2012

69. De Bellis MD, Nooner KB, Scheid JM, Cohen JA : Depression in Maltreated Children and Adolescents. Child Adolesc

Psychiatr Clin N Am 28 : 289-302, 2019

70. Mufson L, Dorta KP, Wickramaratne P, Nomura Y, Olfson M, Weissman MM : A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. Archives of general psychiatry 61 : 577-584, 2004

71. Rosselló J, Bernal G : The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. J Consult Clin Psychol 67 : 734-745, 1999

72. Hazell P, Mirzaie M : Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst Rev 6 : CD002317, 2013

73. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, Hagino OR, Koplewicz H, Carlson GA, Clarke GN, Emslie GJ, Feinberg D, Geller B, Kusumakar V, Papatheodorou G, Sack WH, Sweeney M, Wagner KD, Weller EB, Winters NC, Oakes R, McCafferty JP : Efficacy of paroxetine in the treatment of adolescent major depression : a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 40 : 762-72, 2001

74. von Knorring AL, Olsson GI, Thomsen PH, Lemming OM, Hultén A : A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. Journal of clinical psychopharmacology 26 : 311-315, 2006

75. Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S : Escitalopram in the treatment of adolescent depression : a randomized placebo-controlled multisite trial. J Am Acad Child Adolesc Psychiatry 48 : 721-729, 2009

76. Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA : Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. The American journal of psychiatry 166 : 42-9, 2009

77. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA : Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment : a meta-analysis of randomized controlled trials. JAMA 297 : 1683-1696, 2007

78. Werner-Seidler A, Perry Y, Calear AL, Newby JM, Christensen H : School-based depression and anxiety prevention programs for young people : A systematic review and meta-analysis. Clin Psychol Rev 51 : 30-47, 2017

79. Hetrick SE, Cox GR, Witt KG, Bir JJ, Merry SN : Cognitive behavioural therapy (CBT), third-wave CBT and interpersonal therapy (IPT) based interventions for preventing depression in children and adolescents. Cochrane Database Syst Rev 8 : CD003380, 2016

80. Brent DA, Brunwasser SM, Hollon SD, Weersing VR, Clarke GN, Dickerson JF, Beardslee WR, Gladstone TR, Porta G, Lynch F, Iyengar S, Garber J : Effect of a Cognitive-Behavioral Prevention Program on Depression 6 Years After Implementation Among At-Risk Adolescents : A Randomized Clinical Trial. JAMA psychiatry 72 : 1110-1118, 2015