

DEVELOPMENT AND NATURAL HISTORY OF PEDIATRIC DEPRESSION: TREATMENT IMPLICATIONS

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Summary

Object: To review the literature of the past three decades covering the epidemiology, clinical presentation and natural course of unipolar depression in children and adolescents.

Method: Selected articles published in the past 30 years were reviewed.

Results: The data suggest that pediatric depression is among the most prevalent, recurrent and disabling of all illnesses. Longitudinal investigations showed that early-onset episodes often persist or recur into adulthood. Regardless, these studies also emphasize the variability in clinical course with differing outcomes, including complete recovery, recurrent depressive episodes and development of other psychiatric disorders. There is some indication that different factors predict different clinical outcomes.

Conclusions: Considerable advances have been made regarding our knowledge on the phenomenology and natural course of pediatric depression. Further research is needed in understanding the pathogenesis of early-onset illness. Towards this goal, studies aimed at elucidating mechanisms and interrelationships among the different domains of risk factors are important. Such knowledge will be beneficial in developing more specific and effective treatments for the different subgroups of patients with pediatric mood disorders.

Key Words: Pediatric Depression – Pathogenesis – Early-Onset Illness – Antidepressant Response – Developmental Differences – Unipolar Depression – Children – Adolescents

Declaration of interest: None

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Introduction

The prevalence of depression in children and adolescents is on the rise, and depressive illness during these developmental periods is associated with significant impairment in multiple social domains. Also, there is evidence that early depressive episodes often persist or recur into adult life along with ongoing psychosocial difficulties. This report summarizes research on the development and natural history of pediatric depression. Factors associated with differential longitudinal course of the disorder will be described. Finally, clinical and policy implications of these data will be discussed. A few caveats are warranted before proceeding to the following sections. The term “depression” refers to unipolar mood disorders only. Up to now, most of the research on pediatric depression was conducted in major depressive disorder, and therefore, the reported findings are primarily for this condition. In the majority of studies, children are considered to be 12 years and below and adolescents between 13-18 years.

Prevalence of Unipolar Depression in Youngsters

Prevalence estimates of unipolar depression vary with the time period of reference and method of assessment. The reported point prevalence rates (30-day or 1-year) of major depressive disorder in non-referred samples range between 0.4% and 2.5% in children, and between 0.4% and 8.3% in adolescents (Fleming and Offord 1990, Lewinsohn et al. 1993a, McGee et al. 1992, Reinherz et al. 1993, Kessler et al. 2001). The prevalence rates of depression are much higher in clinical settings, with estimated rates of 8% to 15% in children and from 20% to over 50% in adolescents, depending upon the type of setting (Apter et al. 1988, Wolraich et al. 1996, Schwartz et al. 1998, Teplin et al. 2002, Asarnow et al. 2005). Elevated risk for the disorder begins in the early teens and continues to rise in a linear fashion during adolescent development, with lifetime rates estimated to range from 15% to 25% by late adolescence (Giaconia et al. 1994, Weissman et al. 1997, Hankin et al. 1998, Kessler and Walters 1998).

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These prevalence estimates for pediatric depression are comparable to the lifetime rates reported in adults suggesting that the rates of depression begin to plateau by early adult life (Hankin et al. 1998). These data also suggest that, for a substantial proportion of adult cases, the onset occurred during adolescence (Newman et al. 1996). Moreover, retrospective data from successive cohorts born since World War II suggest that the diagnosis of unipolar depression may be becoming increasingly common and beginning earlier in life (Klerman et al. 1985, Lewinsohn et al. 1993b, Kessler and Walters 1998). Interpreting secular trends is complicated because of increased clinical awareness of pediatric depression and changing diagnostic practices in the decades since World War II. Nevertheless, the recent replication results from the National Comorbidity Survey and some studies of pediatric clinical cohorts are very compelling because adjusted lifetime hazard rates of depression are based on the same interview methods with participants across different age groups ascertained at the same time (Ryan et al. 1992, Kovacs and Gatsonis 1994, Kessler et al. 2005).

Population studies have consistently demonstrated that females are two-to-three times more likely than males to develop depression (Nolen-Hoeksema 1990, Hankin et al. 1998). The female predominance in depression has been observed across many countries and cultures, as well as in cohorts across multiple generations (Kessler et al. 1994, Weissman et al. 1996). A developmental trend has been observed for sex differences in the prevalence rates of depression. Studies in younger children found either no sex difference in rates of depression, or a slight excess in boys (Fleming and Offord 1990, Nolen-Hoeksema et al. 1991). The emergence of gender gap in depression can be traced to a dramatic shift that occurs approximately between the ages of 10 and 14 years, when the precipitous rise in depression rates in girls far exceeds the modest increase observed in boys (McGee et al. 1992, Cohen et al. 1993, Angold et al. 1998, Hankin et al. 1998; Wade et al. 2002). By mid-adolescence, the predominance of depression in females is well established, a trend that continues through young adulthood and middle age (Burke et al. 1990, Kessler et al. 1993, Cohen et al. 1993, Weissman et al. 1997, Hankin et al. 1998). The increased risk for depression in adolescent females is attributed to a complex interplay of psychological and social factors against the background of biological changes (Allgood-Merten et al. 1990, Avison and McAlpine 1992, Brooks-Gunn et al. 1994, Ge et al. 1994, Nolen-Hoeksema and Girgus 1994, Cole et al. 1999, Hankin and Abramson 1999, McCauley-Ohannessian et al. 1999, Wichstrøm 1999, Cyranowski et al. 2000, Stice et al. 2000, Rao 2002).

Clinical Presentation of Pediatric Depression

Dysthymic disorder and major depressive disorder have similar frequency of affective symptoms, but anhedonia and neurovegetative symptoms are less prevalent in dysthymia (Kovacs et al. 1994a). Dysthymia is also associated with an earlier age at onset than major depressive disorder. The clinical syndrome of early-onset depression is remarkably similar to that

of the adult disorder (Roberts et al. 1995, Kovacs 1996, American Psychiatric Association 2000, Ryan 2001, Lewinsohn et al. 2003a). However, there are some developmental differences (Carlson and Kashani, 1988). Specifically, hypersomnia shows a developmental trend with a higher prevalence in depressed adolescents than in children (Ryan et al. 1987, Mitchell et al. 1988). Suicide attempts, particularly those involving high lethality, also increase with age. Melancholic and psychotic symptoms seem to occur less frequently in children, whereas somatic complaints and behavior problems are more common at this developmental period.

In addition to development, sex may have an influence on the severity and symptom profile of depression (Compas et al. 1997). Most of the data on the relationship between sex and symptom patterns are based on data from adults, and there are limited studies in youngsters. In epidemiological and some clinical samples, girls typically reported higher levels of symptoms (Allgood-Merten et al. 1990, Avison and McAlpine 1992, McCauley et al. 1993, Compas et al. 1997, Olsson and von Knorring 1997). With regard to symptom patterns, somatic symptoms, such as changes in appetite and weight, sleep problems and psychomotor retardation are more common in females (Angst and Dobler-Mikola 1984, Baron and Joly 1988, Frank et al. 1988, Young et al. 1990, Carter et al. 2000, Kornstein et al. 2000, Silverstein 2002, Bennett et al. 2005). Increased crying, guilt and other cognitive symptoms also may be more frequent in women (Angst and Dobler-Mikola 1984, Vredenburg et al. 1986, Baron and Joly 1988, Carter et al. 2000, Wilhelm et al. 2002, Bennett et al. 2005). In contrast, depressed males more frequently report melancholic symptoms, social withdrawal and work impairment (Vredenburg et al. 1986, Baron and Joly 1988, Bennett et al. 2005). It is important to note, however, that the findings have been equivocal with regard to the influence of sex on clinical presentation and course of depression (Mitchell et al. 1988, Compas et al. 1997, Simpson et al. 1997, Kovacs 2001; Masi et al. 2001, Lewinsohn et al. 2003a, Sorenson et al. 2005).

Both clinical and epidemiological studies have shown that up to 40% to 70% of children and adolescents with depression also suffer from another psychiatric disorder, and many youngsters have two or more comorbid diagnoses. The most frequent comorbid diagnoses include anxiety disorders, disruptive disorders and substance use disorders (Angold et al. 1999, Kovacs et al. 2003). Although there are insufficient data at present to suggest whether these comorbid patterns of diagnoses represent a developmental sequence, shared genetic or environmental risk factors or a separate subtype of the disorder, it is likely that one or more of these factors contribute significantly to comorbidity. The presence of comorbidity has important clinical and functional implications (Lewinsohn et al. 1995, Sanford et al. 1995, Birmaher et al. 1996a 1996b, Ryan 2001). In particular, youth with comorbid dysthymia and major depression have been found to have more severe and longer depressive episodes, higher frequency of suicidality and social impairment than those who have a single mood disorder (Lewinsohn et al. 1991, Ferro et al. 1994, Kovacs et al. 1984a). Similarly, comorbid anxiety disorder is associated with increased severity and duration of depressive symptoms, increased

suicidality, poor response to psychotherapy and elevated risk for addictive disorders (Brent et al. 1988, Kovacs et al. 1989, Clarke et al. 1992, Kendall et al. 1992, Rao et al. 1999c). In contrast, depressed youth with co-occurring disruptive disorders tend to have fewer melancholic symptoms, fewer recurrent episodes of depression, a lower frequency of familial mood disorders, a higher incidence of criminal behavior and a higher response to placebo than patients with pure depressive illness (Hughes et al. 1990, Biederman et al. 1991, Harrington et al. 1991, 1997). Age and sex can influence the patterns of comorbidity (Cohen et al. 1993, Kovacs et al. 2003). Specifically, separation anxiety disorder and ADHD are more common in children whereas conduct disorder, panic disorder and substance abuse are more common in adolescents (Fleming and Offord 1990, Cohen et al. 1993). Similarly, disruptive and substance use disorders are less likely and eating disorders are more likely in girls than boys (Cohen et al. 1993, Lewinsohn et al. 1993a, Giaconia et al. 1994, Kovacs et al. 2003).

Natural Course of Early-onset Depression

The mean length of a major depressive episode is approximately 6 to 9 months (Kovacs et al. 1984a, Warner et al. 1992, McCauley et al. 1993, Strober et al. 1993, Lewinsohn et al. 1994, Rao et al. 1995). Up to 30% to 40% of patients can be expected to recover by 6 months, and 70% to 80% by 12 months, from the onset (Kovacs et al. 1984a, McCauley et al. 1993, Strober et al. 1993, Lewinsohn et al. 1994, Sanford et al. 1995). Approximately 5% to 10% of patients have a protracted episode, lasting longer than 2 years (McCauley et al. 1993, Kovacs et al. 1997). In contrast to this, recovery from a dysthymic episode appears to be slow. In a prospective study of a clinical sample, only 7% of youth with dysthymia showed evidence of recovery two years after the onset of a first episode (Kovacs et al. 1997). The average duration of a dysthymic episode is 2.5 to 3.5 years (Klein et al. 1988, Lewinsohn et al. 1991, Kovacs et al. 1997). These recovery rates for pediatric depression are comparable to the data in adults (Coryell et al. 1994, Klein et al. 2006, Posternak et al. 2006). Among the baseline demographic and clinical variables that have been examined, none has been shown yet to consistently predict recovery from a depressive episode in youngsters. Age at onset of illness and presence of comorbidity can potentially influence the time to recovery (Warner et al. 1992, McCauley et al. 1993, Lewinsohn et al. 1994, Sanford et al. 1995, Kovacs et al. 1997).

Longitudinal studies of epidemiological and clinical samples have consistently reported that juvenile depression is a recurrent illness, with a probability of recurrence of approximately 40% by two years and 70% by 5 years (Strober and Carlson 1982, Kovacs et al. 1984b, McGee and Williams 1988, Hammen et al. 1990, Warner et al. 1992, Fleming et al. 1993, McCauley et al. 1993, Strober et al. 1993, Lewinsohn et al. 1994, Rao et al. 1995, Sanford et al. 1995). These rates are comparable to the 70% recurrence rate reported in a 5-year prospective study of adult patients with unipolar depression (Coryell et al. 1989). In longitudinal stud-

ies of clinically-referred youths, age and sex did not seem to affect the likelihood of a recurrent depressive episode (McCauley et al. 1993, Kovacs 2001).

In addition to this wealth of information on the clinical course of depression during childhood and adolescence, several studies described the adult sequelae of early-onset depression. The emerging theme from these studies is that early depressive episodes persist into adult life (Garber et al. 1988, Harrington et al. 1990, Kovacs et al. 1994a, Rao et al., 1995, Bardone et al. 1996, Newman et al. 1996, Pine et al. 1998, Lewinsohn et al. 1999, Rao et al. 1999a, Reinherz et al. 1999, Weissman et al. 1999a, 1999b, Fombonne et al. 2001, Aalto-Setala et al. 2002, Ferguson and Woodward, 2002). In addition to recurrent depressive episodes, the depressed youngsters had ongoing psychosocial difficulties, including disruption in interpersonal relationships, early pregnancy, low educational attainment, poor occupational functioning and unemployment, as well as elevated risk for suicidal behavior (Kandel and Davies 1986, Garber et al. 1988, Harrington et al. 1990, Kovacs et al. 1993, Rao et al. 1993, Kovacs et al. 1994b, Rao et al. 1995, Bardone et al. 1996, Newman et al. 1996, Rao et al. 1999a, Reinherz et al. 1999, Weissman et al. 1999a, 1999b, Aalto-Setala et al. 2002, Ferguson and Woodward 2002, Franko et al. 2005). Some studies also reported high rates of psychiatric hospitalizations and mental health services (Harrington et al. 1990, Weissman et al. 1999a, 1999b, McCrone et al. 2005).

Factors Associated with the Differential Course of Pediatric Depression

Although longitudinal investigations of juvenile depression suggest that there is a strong continuity of affective disturbance into adulthood, these studies also have emphasized the variability in clinical course with differing outcomes, including complete recovery, recurrent depressive episodes, and onset of bipolar and substance use disorders (Rao et al. 1995, 1999c, 2000, Geller et al. 2001, Kovacs et al. 2003, Lewinsohn et al. 2003b). There is some indication that different factors predict different outcomes. For example, Harrington et al. (1991) found that depressed youngsters with comorbid conduct disorder were not at increased risk for recurrence of major depressive episodes in adult life as was observed in the depressed subjects without conduct disorder. The longitudinal course in the comorbid group was similar to that of individuals with conduct disorder. Also, adolescent-onset depression, as compared with pre-pubertal onset illness, appears to have a stronger continuity into adulthood (Harrington et al. 1990; Weissman et al. 1999a, 1999b). Other investigators reported that psychotic depression confers increased vulnerability to bipolar disorder among depressed youth (Strober and Carlson 1982, Strober et al. 1993).

In addition to the above described demographic and clinical features, some studies explored biological variables as potential predictors of clinical course of juvenile depression. In particular, electroencephalographic (EEG) sleep and neuroendocrine measures have been studied more extensively in pediatric and

adult depression. In adults, the most reliable EEG sleep changes associated with major depression include sleep continuity disturbances, shorter latency to rapid eye movement (REM) sleep, increased phasic REM sleep and diminished slow-wave sleep (Benca et al. 1992). Similarly, increased cortisol secretion and reduced growth hormone secretion during sleep have been reported consistently in adult depressed patients (Holsboer 1995). Despite having a consonant clinical profile with adult populations, EEG sleep and baseline neuroendocrine changes are observed less frequently in pediatric depression (Kaufman et al. 2001).

Although EEG sleep and neuroendocrine measures did not discriminate depressed youngsters from controls in some cross-sectional studies, these same variables were helpful in predicting differential clinical course (Rao et al. 1996, Coplan et al. 2000, Goetz et al. 2001, Rao et al. 2002, Mathew et al. 2003). For example, we previously reported that the differences between normal adolescent volunteers and depressed youths with respect to EEG sleep findings were masked by vulnerability to depression in the controls and latent bipolar disorder in the depressed cohort. Controls that subsequently developed a depressive episode showed evidence of shortened REM latency and higher REM density long before the onset of depressive illness (Rao et al. 1996), whereas depressed youngsters who switched to bipolar disorder had a normal REM sleep profile (Rao et al. 2002). In contrast to the normal REM sleep profile, depressed youths that developed bipolar disorder had a tendency for reduced slow-wave sleep (Rao et al. 2002). When these two groups were separated from their respective cohorts, depressed youngsters demonstrated the EEG sleep pattern seen in adult depression (Rao et al. 2002). Depression-related EEG sleep markers also have been observed in healthy offspring of depressed patients, and these measures were associated with increased risk for depression on prospective follow-up, suggesting that EEG sleep markers can be useful in identifying those at highest risk for the disorder (Morehouse et al. 2002, Lauer et al. 2004, Modell et al. 2005, Rao et al. unpublished data).

Similar to the EEG sleep measures, baseline measures of nocturnal cortisol and growth hormone predicted first episode of depression in at-risk youths (Coplan et al. 2000, Rao et al. 2003). These neuroendocrine measures also may be helpful in predicting recurrent depressive episodes, suicidal behavior and addictive disorders (Rao et al. 1996, 1999c, Coplan et al. 2000, Mathew et al. 2003). In an investigation of adult participants with identified early-onset depression and in whom the longitudinal clinical course was well-characterized, mid-frontal asymmetry profiles (measured by quantitative EEG) and eye blink responses to affective stimuli were associated with variations in clinical outcome in adult life (Miller et al. 2002, Forbes et al. 2005). These two neurophysiological measures were acquired in adult life, and therefore, the observed changes potentially could be the sequelae of clinical course rather than premorbid markers.

In addition to clinical and biological variables, psychosocial factors, either alone or in concert with biological measures, may be helpful in differentiating the clinical course of pediatric depression (Daley et al.

2000, Lewinsohn et al. 2000, Reiss and Neiderhiser, 2000). For instance, Caspi et al. (2003) found that individuals with one or two copies of the short allele of the serotonin transporter (5-HTT) gene were more likely to develop a depressive episode and/or suicidality after exposure to stressful life events compared with individuals that were homozygous for the long allele of the gene. 5-HTT functional polymorphisms also moderated the effect of childhood maltreatment on depressive disorder in adult life, suggesting that genetic liability interacts with developmental stressors to predict the long-term prognosis of depressive illness (Jaffee et al. 2002, Caspi et al. 2003). We also reported that stressful life events had an additive effect to elevated nocturnal cortisol secretion on time to recovery from a depressive episode and the likelihood of recurrence (Rao et al. 2003). In contrast to this, Kaufman et al. (2004) reported that social support reduced the risk of depressive symptoms in maltreated children with a short allele of the 5-HTT gene.

The Socioeconomic Burden of Pediatric Depression

As described above, there is increasing prevalence of diagnosed depression in youngsters and, in particular, adolescence marks a high risk period for the development of depression. Although the characteristics of depression in youngsters are similar in many respects to those of adult depression, the risk for recurrent depression among youths occurs, on average, about 20 years earlier in their lives (Kovacs 1996). Childhood and adolescent years are crucial periods of life which impact on adult functioning. Consolidation of complex biological and psychosocial maturational processes occurs during this developmental stage. The accumulation of adjustment problems during early life may be especially problematic for future adaptation (Sroufe et al. 1990, Newman et al. 1996, Reinherz et al. 1999, Fergusson and Woodward 2002). Studies in adults have shown that every subsequent depressive episode is associated with more protracted time to recovery and increased risk for recurrence (Keller and Boland 1998). If a similar clinical course occurs in depressed youngsters, at a time when the biological and psychosocial processes have not yet fully matured, then the extent of socioeconomic burden involved with the early-onset illness should be greater than adult depression.

No empirical data are available on the costs to society associated with juvenile depression. However, because early-onset depression marks the gateway into recurrent mood disorders and high rates of service utilization in a substantial proportion of adults, the enormity of the problem can be gleaned from information in adults (Newman et al. 1996, McCrone et al. 2005). Estimates of economic burden in adult depressed patients amount to over 20% of the total costs of all mental illnesses, and the costs exceed \$53 billion per year (Rice and Miller 1995, Hirschfield et al. 1997). According to the estimates made by the World Health Organization, the global burden of disease calculated in terms of disability-adjusted life years, unipolar depression was the leading cause of disability world-wide in the 15- to 44-year age group (World Health Organi-

zation 1996). These data underscore the importance of early identification and appropriate treatment of juvenile depression.

Comparison of Antidepressant Efficacy in Early-onset and Adult-onset Depression

Numerous studies in adults demonstrated the effectiveness of antidepressant agents in the treatment of depression (Charney et al. 1998). Empirical data on the antidepressant efficacy in depressed youngsters have shown marked variability in response rates (for a review, see Cheung et al. 2005). There are no studies directly comparing the antidepressant response between young and adult depressed patients. Data from animal studies indicate maturational differences in the adaptive responses of certain neurobiological systems to repeated antidepressant administration (McCracken and Poland 1995, Carrey et al. 2002). Although data in animals cannot be directly extrapolated to humans, the observed differences might be relevant for understanding age-related differences in antidepressant efficacy.

Information gathered from adult studies also indicates that early-onset depression might be associated with poorer response to antidepressant drugs compared to those who have adult-onset illness (Akiskal et al. 1980, Fava et al. 1997, Alpert et al. 1999, Mulder et al. 2003). Furthermore, preclinical data, showing baseline alterations in the neurobiological systems of adult animals caused by early developmental insults (Rao et al. 1999b), and the changes in the adaptive capacity of these neurobiological systems in response to repeated antidepressant administration (Poland et al. 1995, 1996), suggest parallels with antidepressant response associated with juvenile-onset depression.

Clinical Implications of Developmental Differences in Antidepressant Efficacy

The reasons for differential antidepressant efficacy between depressed youngsters and adults, or among adults with early- versus late-onset illness, are unclear. It is speculated that, because the neurotransmitter systems affected by antidepressant agents continue to develop until late adolescence, and because these systems are quite sensitive to insults during development, this might reduce their ability to mount an "adult-like" adaptive response to antidepressant treatment. Based on the longitudinal studies of pediatric depression, one other possibility is that juvenile-onset depression might be more heterogeneous than the adult form of the disorder. Under this scenario, a subset of depressed youngsters who present with typical clinical and biological features associated with adult depression might benefit most from antidepressant compounds. There is preliminary evidence that depressed youths with reduced REM latency, or those who demonstrate robust REM sleep suppression with traditional antidepressants, respond best to antidepressant drugs (Kupfer et al. 1979, Emslie and Kowatch 1996). Another possibility for the poor antidepressant response in adult patients with early-onset illness is that there may be an interaction between biological processes and clinical course, po-

tentially resulting in less adequate neurobiological adaptation to antidepressant treatment.

Age-related differences in antidepressant effect can have important implications with respect to treatment compliance, prognosis and financial burden. High rate of initial treatment failure is ominous because patients who fail to respond to the first antidepressant trial are at increased risk for not receiving adequate treatment (Katzelnick et al. 1997a), with a potential for reduced treatment compliance during subsequent episodes (Demyttenaere 1997). Also, data from adult studies suggest that residual depressive symptoms increase the risk for early relapse (Faravelli et al. 1986, Maj et al. 1992, Thase et al. 1992, Fava et al. 1994, Paykel et al. 1995, Judd et al. 1998). The elevated risk for relapse associated with partial remission of depressive episodes appears to result from poor treatment response rather than due to inadequate antidepressant treatment (Prien and Kupfer 1986, Georgotas and McCue 1989, Judd et al. 1998). Because many youngsters who seek treatment are in their first depressive episode (Kovacs 1996), and because juvenile depression frequently marks the gateway into recurrent mood disorders in adults, effective treatment during the early phase of illness can minimize the long-term negative consequences of depressive episodes. Additionally, more effective initial treatment of depression has the potential advantage of reducing health care costs through decreased utilization of psychiatric and medical services, and diminished expenditure related to ineffective medication costs (Katzelnick et al. 1997b). Therefore, a better understanding of the mechanisms associated with developmental differences in antidepressant efficacy potentially might be helpful in developing more effective antidepressant agents for juvenile depression, as well as for adult patients with inadequate response to the traditional treatments.

In addition to investigating the effects of antidepressant drugs, psychosocial interventions, alone and in conjunction with antidepressant agents, should be tested. As described above, psychosocial factors have a moderating influence on the development and course of depression in youngsters (Caspi et al. 2003, Rao et al. 2003, Kaufman et al. 2004). Also, cognitive-behavioral and interpersonal therapies have demonstrated efficacy in the treatment and prevention of pediatric depression (Mufson et al. 2004, Clarke et al. 2005, Hamrin and Pachler 2005, Pathak et al. 2005). The development of more specific and effective intervention(s) for the different subgroups of depressed youths will likely have a significant impact on the prognosis.

Summary

Pediatric depression is of great public health significance, with serious morbidity and mortality, thereby emphasizing the need for early identification and effective treatment strategies. In the past three decades, considerable advances have been made regarding our knowledge on the phenomenology and natural course of juvenile depression. However, additional research is needed in understanding the pathogenesis of early-onset illness. In particular, studies aimed at elucidating

mechanisms and interrelationships among the different domains of risk factors are important. Such knowledge will be beneficial in developing more specific and effective treatments for the different subgroups of patients with pediatric mood disorders.

Despite the similarities between juvenile and adult depression in clinical presentation, patterns of comorbidity and longitudinal course, developmental differences have been noted with respect to antidepressant response. Adult patients with early-onset depression also appear to have reduced antidepressant effect than those with later-onset illness. Based on the observed age-related differences in neurobiological markers associated with depressive disorder, it is hypothesized that there might be developmental differences in the adaptive capacity of certain neurobiological systems in response to antidepressant treatment. Therefore, knowledge gained from studying the mechanisms associated with developmental differences in antidepressant response potentially might be helpful in developing more effective antidepressant drugs for juvenile depression, and for treatment-resistant depression in adults as well.

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