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## Pediatric depression: is there evidence to improve evidence-based treatments?

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### Abstract

Although there have been advances in our ability to treat child and adolescent depression, use of evidence-based treatments still results in many patients with residual symptoms. Advances in our understanding of cognitive, emotional, and ecological aspects of early-onset depression have the potential to lead to improvements in the assessment and treatment of depression. A search for endophenotypes, i.e., traits that are related to depression, mediate the familial transmission of depression, and are genetically determined, may help in understanding etiology and in personalizing treatment. However, advances in treatment may also come from the identification of biomarkers, i.e., modifiable neurocognitive, physiological, or biochemical indices that are correlated with, or mediate, treatment outcome. More effective treatments may emerge from being able to personalize interventions to the patient's cognitive, emotional, and developmental profile.

### Keywords

Depression; cognition; development; treatment; intermediate phenotype; biomarker

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Depression in childhood and adolescence is a chronic, recurrent, and impairing condition associated with increased psychosocial and medical morbidity and mortality (Kovacs, 1996; Lewinsohn, Rohde, & Seeley, 1998). Advances have been made in identifying possible cognitive, and emotional phenotypic components of depression, but there has been little 'cross-talk' between these lines of investigation and intervention research. While treatments have been demonstrated to improve outcome in many depressed youth, a significant minority do not show complete symptomatic remission or even an adequate clinical response (Bridge et al., 2007; Weisz, McCarty, & Valeri, 2006).

In this paper, we briefly review recent progress in the characterization of phenotypic and possibly etiological domains, critique the extant intervention literature, identify potentially fruitful areas of inquiry and offer recommendations for next steps in descriptive and intervention research for depressed youth. We discuss two categories of characteristics of depressed youth that may be helpful in improving treatment. An endophenotype is a heritable, state-independent trait that is associated with a disease, co-segregates with the

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disease, and is found in non-affected family members at a higher rate than in the population (Gottesman & Gould, 2003). A biomarker is a 'biological identifier of a natural process which correlates with a clinical outcome or a surrogate endpoint' (Levenson, 2004). Whereas endophenotypes and other non-modifiable characteristics of patients, like ethnicity and family constellation, may be helpful in identifying subgroups of individuals who may be best served by particular interventions, the identification of biomarkers may be helpful in monitoring, and optimizing, treatment response.

## **Domains of risk**

### **Developmental epidemiology**

The point prevalence of depression in children is 1–2%, increasing to 3–8% in adolescents. By the end of adolescence, approximately 1 in 5 adolescents will have experienced at least one depressive episode (Lewinsohn et al., 1998). After the onset of puberty, girls have twice the risk of developing depression that boys do, and risk is closely correlated with levels of testosterone, estradiol, and follicular stimulating hormone (Angold, Costello, Erkanli, & Worthman, 1999).

Developmental changes in the social ecology of youth as they enter adolescence that may predispose to depression include decreased adult supervision and support, increased concern about social status and social rejection, increased parent–child conflict, and lifestyle changes that can predispose to depression, such as substance use and sleep deprivation (Nelson, Leibenluft, McClure, & Pine, 2005; Dahl, 2004).

### **Neurocognitive**

Youth at risk for depression and depressed youth show cognitive bias towards negative emotion in both self-report and laboratory-based tests (Perez-Edgar, Fox, Cohn, & Kovacs, 2006; Joormann, Talbot, & Gotlib, 2007). Depressed youth show faster orienting to probes with a negative valence (e.g., emotional faces and sad words) along with cognitive disruption of processing by such probes (Ladouceur et al., 2006; Kyte, Goodyer, & Sahakian, 2005; Ladouceur et al., 2005; Perez-Edgar et al., 2006). The relationship between cognitive bias and depression may be mediated by difficulties in self-distraction, set-shifting, and by tendency to engage in rumination (Park, Goodyer, & Teasdale, 2004; Wilkinson & Goodyer, 2006). Depressed youth compared to healthy controls showed diminished late pupillary dilatation in response to negatively-valenced words, consistent with initial avoidance of negative emotional stimuli (Silk et al., 2007b). Overgeneral categorical autobiographical memory, with difficulty accessing specific emotionally valenced memories, may represent difficulty in encoding, or in retrieval, which in turn may predict recurrence of depression (Park et al., 2004; Park, Goodyer, & Teasdale, 2002).

### **Positive affect and reward**

Positive affect involves reward anticipation and the ability to experience pleasure and joy. Depressed youth are less likely to respond to reward incentives (Hardin, Schroth, Pine, & Ernst, 2007) and, by ecological momentary assessment (EMA), show lower levels of self-reported positive affect (Silk et al., 2007a). When faced with a reward-contingent decision

task, depressed youth are less likely to choose an option with high probability of a high magnitude reward and show lower activation in reward-related brain areas while performing such tasks (Forbes et al., 2006b; Forbes, Shaw, & Dahl, 2007). Low levels of positive affect and reward-orientation are predictive of onset and recurrence of depression (Forbes et al., 2006b; Forbes et al., 2007). Conversely, positive reward anticipation buffers the relationship between maternal history of depression and offspring internalizing symptoms (Silk, Shaw, Skuban, Oland, & Kovacs, 2006).

### Emotion regulation

Emotion regulation can refer to the magnitude and duration of physiological arousal. With regard to the former, depressed adolescents show higher cortisol levels measured close to sleep onset (Forbes et al., 2006c). Depressed youth have reported to have either decreased (Thomas et al., 2001) or increased amygdala reactivity to emotional faces (Roberson-Nay et al., 2006), with the latter study controlling for the difficulty depressed youth have in encoding facial memory (Pine, 2004). Young offspring of mothers with early-onset depression show lower resting respiratory sinus arrhythmia and increased heart rate in response to frustration (Forbes, Fox, Cohn, J., Galles, & Kovacs, 2006a). Adolescent female offspring of depressed parents show increased cortisol secretion in response to social stress (Halligan, Herbert, Goodyer, & Murray, 2004, 2007).

Alternatively, emotion regulation can refer to the *strategies* with which an individual engages in order to modulate emotional response to provocation or frustration. Depressed youth are slower at switching attention (Wilkinson & Goodyer, 2006), and those predisposed to depression show use of greater cognitive resources when exposed to emotional stimuli (Perez-Edgar et al., 2006). Offspring of depressed parents show decreased ability to use distraction, cognitive shifting, and positive memories and are more likely to passively withdraw in the face of frustration or induction of sad mood (Forbes et al., 2006a; Silk et al., 2006).

### Parental depression and genetics

Offspring of depressed parents are at increased risk for a depressive episode, with greater risk being associated with greater family loading for depression, earlier parent age of onset, and recurrent depression in parents (Weissman et al., 2006b). Greater family loading for depression is associated with earlier onset in offspring, higher rates of comorbid anxiety, and greater risk of chronicity (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Weissman et al., 2006b). Twin studies find greater heritability for adolescent vs. childhood onset depressive symptoms, and co-transmission of depression and anxiety symptomatology (Thapar & McGuffin, 1997). The less functional variant of the serotonin transporter gene is associated with early-onset depression, especially in concert with environmental stress (Caspi et al., 2003). In addition, this genetic variant has been shown to be related to biological correlates of depression and anxiety, such as amygdala reactivity to emotional faces (Hariri et al., 2002), and cortisol hypersecretion to social stress (Gotlib, Joormann, Minor, & Hallmayer, in press).

## Family interaction

Depression in parents conveys increased risk for depression in their offspring, through environmental as well as heritable pathways. High levels of expressed emotion and parent-child discord have been associated with the onset, recurrent, and prolongation of depressive episodes (Silk et al., in press; Emslie et al., 1998). Mothers with a history of depression, compared to control mothers, are less engaged with their children during a problem-solving task, are less responsive to their children's emotional distress, and promote fewer emotion regulation strategies in their children (Shaw et al., 2006). Conversely, treatment of maternal depression may protect unaffected children against disorder and improve the outcome of children currently in mental health treatment (Weissman et al., 2006a; Swartz et al., in press). EMA assessments demonstrate that depressed children and adolescents spend less time with their families than do their non-depressed counterparts (Silk et al., 2007a). The quality and quantity of parental involvement can be protective against depression and other adverse health and mental health outcomes (Resnick et al., 1997).

## Early experiences

The quality of early parental care can affect risk for depression and a wide range of health outcomes (Felitti et al., 1998). Children whose mothers have experienced a perinatal depression have higher cortisol levels, which mediates the relationship between maternal and offspring depressive symptoms (Halligan et al., 2004, 2007). However, abuse has been reported to be associated with a less vigorous cortisol response to social stress (Heim et al., 2002) and lower salivary cortisol (Kaufman, 1991). Early deprivation can result in lower central serotonergic function, which in turn is associated with impulsive aggression, depression, and suicidal behavior (O'Connor & Cameron, 2006). Low birth weight and early maternal age have also been reported as risk factors for the development of depression, especially in females (Lewinsohn et al., 1998; Costello, Worthman, Erkanli, & Angold, 2007).

## Life events

Independent life events, such as parental loss, are risk factors for depression. Dependent life events, e.g., those generated by the youth at risk for depression, appear to be conflated with genetic risk for depression (Eaves, Silberg, & Erkanli, 2003). Youth belonging to an antisocial peer group are at increased risk for depression, because of the likelihood of incurring depressogenic life events like parent-child conflict, disciplinary and legal problems (Fergusson & Lynskey, 1996).

## Sleep

Depressed youth report more subjective sleep difficulties than healthy controls, but show few objective indicators of disturbed sleep (Forbes et al., 2008). By objective measures, difficulty falling asleep and shorter total sleep are more closely associated with anxiety disorders, and may partially explain the increased risk for depression in those with anxiety disorders (Forbes et al., 2008).

## Peer relationships

Interpersonal relationships often are precipitants for depression, particularly in adolescents. EMA assessment shows that depressed adolescents spend more time with their friends than do their non-depressed counterparts, but also that they experience more negative emotion when with peers, perhaps due to assortative friendships that reinforce negative emotion (Silk et al., 2007a).

## School and activities

Depressed youth are less likely to engage in pleasurable activities and have a less positive connection to schoolwork and activities (Lewinsohn et al., 1998). As symptoms of depression include impaired motivation and concentration, school work is often negatively affected, and the long-term prognosis of untreated depression includes educational and occupational under-achievement (Lewinsohn et al., 1998; Fergusson & Woodward, 2002; Kovacs, 1996).

## Health risk behaviors

Depressed youth often have concomitant health risk behaviors, including tobacco and substance abuse, overeating and obesity, low physical activity, engagement in unprotected sex, and antisocial behavior, all of which have the potential to precipitate or prolong a depressive episode, to affect long-term health and functional status (Brooks, Harris, Thrall, & Woods, 2002).

## Interventions

### Antidepressants

**Efficacy**—A recent meta-analysis of all FDA-registered placebo-controlled clinical trials for pediatric depression found a modest but significant advantage of drug over placebo (number needed to treat [NNT] = 10) (Bridge et al., 2007). For the treatment of depressed adolescents who have not responded to an initial adequate trial with an SSRI, a switch to another SSRI was just as efficacious as a switch to venlafaxine, with fewer side effects (Brent et al., 2008). While response and sustained improvement occurs in well over half of treatment-naïve depressed adolescents, complete symptomatic remission rates are considerably lower, on the order of 20–37% after 12 weeks of treatment (Kennard et al., 2006).

**Mechanism of action**—SSRI antidepressants work by inhibiting reuptake of serotonin by pre-synaptic neurons, with at least 70% reuptake inhibition required to result in clinical improvement (Axelson et al., 2005; Lesch, Wolozin, Murphy, & Reiderer, 1993). Studies in adults show that antidepressants increase dorsal prefrontal activity and decrease limbic activity, which allows for emotional modulation.

**Developmental issues**—Antidepressants are more efficacious in adolescents than in children (NNT of 7 vs. 15), except for studies of fluoxetine, in which the effects are equal in children and in adolescents. The half-lives of paroxetine, sertraline, citalopram, and venlafaxine are shorter in children and adolescents than in adults (Findling et al., 2006),

which may explain the superior efficacy of fluoxetine vs. these other agents in prepubertal youth. Also, pre-pubertal youth with depression often present with comorbid conduct disorder, a negative family history, high levels of familial adversity and a course that resembles pure conduct disorder, which may account for the high placebo response rate in prepubertal depression.

**Predictors and moderators of treatment outcome**—Higher amygdala activity predicts better response to fluoxetine in anxious youth (McClure et al., 2007). Depressed and anxious youth homozygous for the more functional 1 allele of the serotonin transporter promoter gene are more likely to respond to citalopram (Kronenberg et al., 2007). Family discord lowers the probability of antidepressant response (Emslie et al., 1998). Other clinical predictors of poor outcome include chronicity, comorbidity, and baseline severity (Curry et al., 2006), although the difference between placebo and medication is greatest in more severely ill depressed youth (Bridge, Birmaher, Iyengar, Barbe, & Brent, 2008).

**Suicidality**—Antidepressants increase the risk of a spontaneously reported suicidal adverse events by about 2-fold, with estimates of the risk difference ranging between .9–2% (Bridge et al., 2007). Most of these suicidal adverse events were increases in suicidal ideation, with relatively few attempts, and no completions. Twelve times more depressed youth show a clinical response than experience a suicidal event (Bridge et al., 2007). The use of antidepressants and the diagnosis of depression has dropped in pediatric populations, especially in primary care, without any counterbalancing increase in referrals for psychotherapy (Libby et al., 2007). More concerning, after more than a decade of steady decline in the adolescent suicide rate, some, but not all countries show a one-year increase in adolescent suicide (Gibbons et al., 2007).

Those depressed youth with high suicidal ideation, irritability, or anger have been reported to be at higher risk for a suicidal adverse event (Emslie et al., 2006). While disinhibition, switch to mania, onset of akathisia, increased irritability, and non-adherence followed by withdrawal from medication have all been posited to be related to suicidal adverse events, none of these hypotheses have been tested in pediatric samples. The ability to identify those who are most likely to respond and least likely to have adverse events is critical to any dissemination efforts, given the current level of concern about these medications.

**Prevention of relapse**—Continuation treatment with antidepressant medication prevents depressive relapse over 6 months after symptomatic improvement (Emslie et al., 2008). Protection against relapse was particularly effective in those youth who had already attained complete remission.

## Psychotherapy

**Efficacy**—CBT consists of an amalgam of techniques, including behavior activation, cognitive restructuring, emotion regulation, problem solving, and skills training. Its effects in depression are significant, but modest ( $d = .35$ ) (Weisz et al., 2006). CBT monotherapy was not superior to pill-placebo, and markedly inferior to fluoxetine for the acute treatment of adolescent depression (The TADS Team, 2004). Interpersonal therapy (IPT) is superior to

clinical management or treatment as usual, and equal or superior to CBT, but has not been tested against pill-placebo, medication, or combination treatment (Klomek & Mufson, 2006; Rossello & Bernal, 1999). The combination of CBT and medication has been found to be superior to medication alone for the achievement of remission (Kennard et al., 2006; Brent et al., 2008). However, in the Adolescent Depression, Antidepressants and Psychotherapy Trial (ADAPT), no difference was found between combination treatment and medication monotherapy (Goodyer et al., 2007). The divergence in findings between the Treatment of Adolescent Depression Study (TADS) and the Treatment of SSRI-resistant Depression in Adolescents (TORDIA) on one hand, and ADAPT on the other, may be due to differences in sampling frame and design. ADAPT's participants were severely depressed adolescents who did not respond to a brief psychosocial intervention, characteristics that have been shown to decrease the likelihood of response to combination treatment in other samples (Curry et al., 2006).

**Mechanism of action**—CBT in adults has been shown to result in an increase in anterior cingulate activity, consistent with improved cognitive control over affect (Fu et al., 2008). Decrease in cognitive distortions, and increased participation in positive activities mediated improvement in depressive symptoms (Weersing & Brent, 2006; Lewinsohn et al., 1998). No formal tests of mediation have been conducted with IPT, but it has been shown to improve social functioning and interpersonal problem-solving (Klomek & Mufson, 2006).

**Developmental considerations**—CBT has been used in both pre-adolescents with depressive symptoms and diagnosed and clinically referred adolescents. While family conflict is central to onset and maintenance of depressive symptoms, CBT treatments that have added a family component have not necessarily been more successful (Lewinsohn et al., 1998; The TADS Team, 2004). In contrast, IPT's focus on interpersonal relationships with family and peers fits with the primary developmental tasks and common precipitants for depression in childhood and adolescence. IPT's focus on attenuating the impact of stressful life events is consistent with current views of gene by environment interactions in the pathogenesis of depression (Caspi et al., 2003).

**Predictors and moderators of outcome**—Higher amygdala activity predicts response to CBT in pediatric anxiety (McClure et al., 2007). Higher levels of cognitive distortions and greater depressive severity have predicted poorer response to CBT, although a higher level of cognitive distortion was a *positive* moderator of outcome for combined treatment in the TADS study (Curry et al., 2006; Weersing & Brent, 2006). Family conflict, a history of abuse, and current maternal depression predict a poorer response to CBT. Positive moderators for CBT outcome include comorbid anxiety and higher family income. IPT shows a greater benefit over a comparison treatment for those with greater severity of depression, and with comorbid anxiety (Young, Mufson, & Davies, 2006).

**Suicidality**—In TADS, but not in other studies (Brent et al., 2008; Goodyer et al., 2007), combination treatment produced the most rapid reduction in suicidal ideation and showed a trend towards having lower numbers of suicidal events in acute treatment (Emslie et al.,

2006; The TADS Team, 2004). IPT was not different from clinical management in the reduction in suicidal ideation or events (Klomek & Mufson, 2006).

**Prevention of relapse and onset**—The rate of relapse after acute treatment with CBT appears to be high unless booster sessions are administered (Weersing & Brent, 2006). The TADS study reported an increasing rate of clinical response in CBT alone over time, with no differences between the combined treatment, CBT, and the fluoxetine groups at 9 months post-treatment (The TADS Team, 2007). These results suggest that longer and more intensive treatment can result in a high rate of sustained recovery, but this conclusion would be strengthened if there were a comparison group to control for the rate of spontaneous recovery. Group CBT and group IPT has been efficacious in the prevention of onset of depression in youth at increased risk for depression due to family or personal history of depression and/or subsyndromal depression (Weersing & Brent, 2006).

**Dissemination of evidence-based treatments**—IPT delivered by school counselors resulted in a higher rate of improvement of depression than usual care in school-based clinics (Klomek & Mufson, 2006). A quality improvement study based in primary care that allowed for depressed adolescents to choose CBT and/or pharmacotherapy resulted in most participants opting for CBT, and found a modest improvement over usual care (Weersing & Brent, 2006; Asarnow et al., 2005). Barriers against dissemination of pharmacotherapy include patient preference and patient, family, and practitioner concerns about suicidal events associated with antidepressant treatment, the latter of which warrants further study.

## Conclusions and recommendations

Much progress has been made in the identification of potential endophenotypes for depressive disorder, such as cognitive bias, low positive affect and reward orientation, and emotional dysregulation. However, few research groups use the same protocol, making it very difficult to compare results across studies. The schizophrenia scientific community's development of common probes for the study of neuropsychological functioning in schizophrenia may serve as a useful template for depression researchers (Green et al., 2008). Samples are often small and heterogeneous with respect to current symptomatology and comorbidity, which makes it difficult to disentangle trait from state characteristics. It would be of interest to understand how different domains interrelate; when studies have bridged domains, some of the payoffs are rich – as in the relationship between the less functional serotonin promoter gene variant and cortisol secretion and amygdala activation (Gotlib et al., in press; Hariri et al., 2002). Measures that are state- or biomarkers of depression, such as neurocognitive deficits, may be useful to identify youth at risk for relapse, and to modify treatment for those who fail to respond (Majer et al., 2004; Siegle, Ghinassi, & Thase, 2007).

We can use what has been learned about predictors and moderators of treatment response to ameliorate our results right now. Combination treatment appears to result in more rapid and/or more complete response than monotherapy in most, but not all studies (Brent et al., 2008; Goodyer et al., 2007; The TADS Team, 2004). Longer duration treatment is likely to consolidate treatment response and prevent relapse (Emslie et al., 2008; The TADS Team,

2007). Assessment and treatment of maternal depression can improve treatment outcome (Weissman et al., 2006a; Swartz et al., in press). In patients with comorbid anxiety both CBT and IPT have been shown to be of benefit (Young et al., 2006; Weersing & Brent, 2006). While poor response to CBT is predicted by a lower income, IPT has been successfully implemented in samples of low income, minority youth (Klomek & Mufson, 2006; Rossello & Bernal, 1999).

Prioritizing use of antidepressants for youth with moderate to severe depression could improve the benefit-to-risk ratio. We lack dose-response studies in depressed youth that could clarify the relationship between exposure and outcome, and facilitate rational dosing of youth with antidepressants. Biomarkers such as serotonin reuptake inhibition may serve as proxy endpoints for treatment response, and allow for more precise titration of dosage. Some relatively simple ways to individualize treatment would be to identify patients who are at risk for inadequate exposure to medication, either due to non-adherence, or rapid metabolism, and, on the basis of drug level monitoring, titrate their dosage accordingly. Given the likely high rate of non-adherence to medication regimens, additional patient education and motivational interviewing may be indicated. Non-pharmacological management of sleep difficulties may also boost response rates to antidepressant treatment (Brent et al., 2008). Finally, further study of the pharmacological agents to increase the pace of response is indicated in order to decrease the hazards of continued depression (Zarate et al., 2006; Sallee, Vrindavanam, Deas-Nesmith, Carson, & Sethuraman, 1997).

Response to selected emotional stimuli that distinguish suicide attempters from non-attempters in a sample of depressed patients suggest that interventions that target emotion regulation may reduce the risk for suicidal events during treatment with an antidepressant (Jollant et al., 2008). Pharmacogenetic profiling may help to identify individuals most likely to respond and less likely to experience suicidal adverse events (Laje et al., 2007) and cognitive measures of preoccupation with suicidal ideation such as the Implicit Association Test may be useful in monitoring risk for suicidal events (Nock & Banaji, 2007).

Optimization of treatment response may be achieved via biomarkers of treatment response, such as anterior cingulate or amygdala activity in response to negatively-valenced emotional stimuli. Although neuroimaging may not be a practical tool to add to a large-scale clinical trial, there are off-line measures of emotion reactivity that may serve as surrogates, such as pupillometry (Silk et al., 2007a). One promising approach that translates the neurocognitive observations of difficulty with attention and set-shifting into an intervention for chronic depression is Cognitive Control Training (Siegle et al., 2007).

The overall effects of child and adolescent depression treatment have been modest, perhaps due to a mismatch between current treatment approaches and the developmental psychopathology of depression. Cognitive distortions become more fixed outside of depressive episodes during adolescence, which may limit the efficacy of CBT in younger populations. Youth are most concerned about their relationships with their family, their peers, and school. Although these concerns are often topics within CBT, this treatment does not explicitly target domains known to influence outcome, such as family conflict, parental depression, peer relationships, and the make-up of the child's peer group. CBT tends to

focus on the cognitive mode of emotion regulation, with a secondary emphasis on behavior activation or interpersonal modes of emotion regulation, despite equal or greater evidence for the efficacy of the latter two approaches (Kovacs et al., 2006). Moreover, high levels of cognitive distortion in most studies predict a poorer response to CBT, perhaps because cognitive bias, while partially modifiable, may be a trait rather than a state marker of depression. Better outcomes may be obtained by careful assessment of the child's neurocognitive and emotional regulation profile, and matching treatment strategy to those deficits most easily modified. In the absence of such assessment tools, some depressed youth may respond better to alternative emotion regulation techniques such as engaging in physical activity and in other rewarding behaviors, and practicing use of distraction, set-shifting, and accessing positive memories (Siegle et al., 2007).

While IPT focuses also primarily on the interpersonal mode for achieving emotion regulation, it is an accessible and easily grasped treatment because most youth have interpersonal concerns. In the only head-to-head comparison of IPT and CBT for depressed youth, results were similar except for greater improvement in social functioning in IPT (Rossello & Bernal, 1999). IPT may have more limited applicability if other means of emotion regulation are more beneficial for the individual (Weersing & Brent, 2006). Interventions that also focus on the youth's social ecology, such as the make-up of his or her peer group, and the connection to school may also be useful, given previous research (Resnick et al., 1997).

An overarching critique of all interventions for youth depression is that they tend to ignore concomitant health risk behaviors, such as substance use, having unprotected sex, overeating, low levels of physical activity, and high stress-reactivity. Engagement in physical activity, improving sleep and emotion regulation and decreasing impulsivity may be interventions that can both ameliorate depression and reduce risks for serious chronic physical conditions such as cardiovascular disease. A broader focus on common causes for depression and related health concerns, both in etiological and in intervention research could help us help our young depressed patients to lead healthier, more fulfilling, and more productive lives.

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## References

- Angold A, Costello EJ, Erkanli A, Worthman CM. Pubertal changes in hormone levels and depression in girls. *Psychological Medicine*. 1999; 29:1043–1053. [PubMed: 10576297]
- Asarnow JR, Jaycox LH, Duan N, LaBorde AP, Rea MM, Murray P, et al. Effectiveness of a quality improvement intervention for adolescent depression in primary care clinics a randomized controlled trial. *Journal of the American Medical Association*. 2005; 293:311–319. [PubMed: 15657324]
- Axelson DA, Perel JM, Birmaher B, Rudolph G, Nuss S, Yurasits L, et al. Platelet serotonin reuptake inhibition and response to SSRIs in depressed adolescents. *American Journal of Psychiatry*. 2005; 162:802–804. [PubMed: 15800159]

- Brent DA, Emslie GJ, Clarke GN, Wagner KD, Asarnow J, Keller MB, et al. Switching to venlafaxine or another SSRI with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized control trial. *Journal of the American Medical Association*. 2008; 299:901–913. [PubMed: 18314433]
- Bridge J, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus H, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association*. 2007; 297:1683–1696. [PubMed: 17440145]
- Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA. Placebo response in randomized, controlled trials of antidepressants for pediatric major depressive disorder. *American Journal of Psychiatry*. 2008 Manuscript submitted for publication.
- Brooks TL, Harris SK, Thrall JS, Woods ER. Association of adolescent risk behaviors with mental health symptoms in high school students. *Adolescent Health*. 2002; 31:240–246.
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HT gene. *Science*. 2003; 301:386–389. [PubMed: 12869766]
- Costello EJ, Worthman C, Erkanli A, Angold A. Prediction from low birth weight to female adolescent depression. *Archives of General Psychiatry*. 2007; 64:338–344. [PubMed: 17339522]
- Curry J, Rohde P, Simons S, Silva S, Vitiello B, Kratochvil C, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *Archives of General Psychiatry*. 2006; 45:1427–1439.
- Dahl, RE. Regulation of sleep and arousal: Comments on Part VII. In: Dahl, RE.; Spear, LP., editors. *Adolescent Brain Development: Vulnerabilities and Opportunities*. New York Academy of Sciences; New York: 2004. p. 292-293.
- Eaves L, Silberg J, Erkanli A. Resolving multiple epigenetic pathways to adolescent depression. *Journal of Child Psychology and Psychiatry*. 2003; 44:1006–1014. [PubMed: 14531583]
- Emslie G, Kratochvil C, Vitiello B, Silva S, Mayes T, McNulty S, et al. Treatment for Adolescents with Depression Study (TADS): Safety results. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45:1440–1455. [PubMed: 17135989]
- Emslie GJ, Kennard BD, Mayes TL, Nightingale J, Carmody T, Hughes CW, et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *American Journal of Psychiatry*. 2008; 165:459–467. [PubMed: 18281410]
- Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Carmody T, Mayes TL. Fluoxetine in child and adolescent depression: Acute and maintenance treatment. *Depression and Anxiety*. 1998; 7:32–39. [PubMed: 9592630]
- Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. *American Journal of Preventive Medicine*. 1998; 14:245–258. [PubMed: 9635069]
- Fergusson DM, Lynskey MT. Adolescent resiliency to family adversity. *Journal of Child Psychology and Psychiatry*. 1996; 37:281–292. [PubMed: 8707911]
- Fergusson DM, Woodward LJ. Mental health, educational, and social role outcomes of adolescents with depression. *Archives of General Psychiatry*. 2002; 59:225–231. [PubMed: 11879160]
- Findling RL, McNamara NK, Stansbrey RJ, Feeny NC, Young CM, Peric FV, et al. The relevance of pharmacokinetic studies in designing efficacy trials in juvenile major depression. *Journal of Child and Adolescent Psychopharmacology*. 2006; 16:131–145. [PubMed: 16553534]
- Forbes EE, Bertocci MA, Gregory AM, Ryan ND, Axelson DA, Birmaher B, et al. Objective sleep in pediatric anxiety disorders and major depressive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2008; 47:148–155. [PubMed: 18176336]
- Forbes EE, Fox NA, Cohn J, Galles S, Kovacs M. Children's affect regulation during a disappointment: Psychophysiological responses and relation to parent history of depression. *Biological Psychiatry*. 2006a; 71:264–277.

- Forbes EE, May C, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, et al. Reward-related decision-making in pediatric major depressive disorder: An fMRI study. *Journal of Child Psychology and Psychiatry*. 2006b; 47:1031–1040. [PubMed: 17073982]
- Forbes EE, Shaw DS, Dahl RE. Alterations in reward-related decision making in boys with recent and future depression. *Biological Psychiatry*. 2007; 61:633–639. [PubMed: 16920074]
- Forbes EE, Williamson DE, Ryan ND, Birmaher B, Axelson DA, Dahl RE. Peri-sleep-onset cortisol levels in children and adolescents with affective disorders. *Biological Psychiatry*. 2006c; 59:24–30. [PubMed: 16112658]
- Fu CH, Williams SC, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biological Psychiatry*. 2008 Epub [ahead of print].
- Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry*. 2007; 164:1356–1363. [PubMed: 17728420]
- Goodyer I, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: Randomised controlled trial. *British Medical Journal*. 2007; 335:106–107. [PubMed: 17641303]
- Gotlib IH, Joormann J, Minor KL, Hallmayer J. HPA axis reactivity: A mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biological Psychiatry*. in press.
- Gottesman I, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Green MF, Nuechterlein KH, Kern RS, Baade LE, Fenton WS, Gold JM, et al. Functional co-primary measures for clinical trials in schizophrenia: Results from the MATRICS Psychometric and Standardization Study. *American Journal of Psychiatry*. 2008; 165:221–228. [PubMed: 18172017]
- Halligan SL, Herbert J, Goodyer I, Murray L. Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biological Psychiatry*. 2007; 62:46.
- Halligan SL, Herbert J, Goodyer IM, Murray L. Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. *Biological Psychiatry*. 2004; 55:381.
- Hardin MG, Schroth E, Pine DS, Ernst M. Incentive related modulation of cognitive control in healthy anxious and depressed adolescents development and psychopathology related differences. *Journal of Child Psychology and Psychiatry*. 2007; 48:446–454. [PubMed: 17501725]
- Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002; 297:400–403. [PubMed: 12130784]
- Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB. The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: A multiple regression analysis. *Depression and Anxiety*. 2002; 15:117–125. [PubMed: 12001180]
- Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, et al. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. *American Journal of Psychiatry*. 2008 Epub.
- Joormann J, Talbot L, Gotlib IH. Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology*. 2007; 116:135–143. [PubMed: 17324024]
- Kaufman J. Depressive disorders in maltreated children. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1991; 30:257–265. [PubMed: 2016230]
- Kennard B, Silva S, Vitiello B, Curry J, Kratochvil C, Simons A, et al. Remission and residual symptoms after short term treatment in the treatment of adolescents with depression studt-tads. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45:1404–1411. [PubMed: 17135985]
- Klein DN, Lewinsohn PM, Rohde P, Seeley JR, Olinio TM. Psychopathology in the adolescent and young adult offspring of a community sample of mothers and fathers with major depression. *Psychological Medicine*. 2005; 35:353–365. [PubMed: 15841871]

- Klomek AB, Mufson L. Interpersonal psychotherapy for depressed adolescents. *Child and Adolescent Psychiatric Clinics of North America*. 2006; 15:959–975. [PubMed: 16952770]
- Kovacs M. Presentation and course of major depressive disorder during childhood and later years of the life span. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1996; 35:705–715. [PubMed: 8682751]
- Kovacs M, Sherril J, George CJ, Pollock M, Tumuluru RV, Ho V. Contextual emotion-regulation therapy for childhood depression: Description and pilot testing of a new intervention. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45:892–903. [PubMed: 16865031]
- Kronenberg S, Apter A, Brent D, Schirman S, Melhem N, Pick N, et al. Serotonin transporter polymorphism (5-HTTLPR) and citalopram effectiveness and side effects in children with depression and/or anxiety disorders. *Journal of Child and Adolescent Psychopharmacology*. 2007; 17:741–750. [PubMed: 18315446]
- Kyte Z, Goodyer I, Sahakian BJ. Selected executive skills in adolescents with recent first episode major depression. *Journal of Child Psychology and Psychiatry*. 2005; 46:995–1005. [PubMed: 16109002]
- Ladouceur CD, Dahl RE, Williamson DE, Birmaher B, Axelson D, Ryan ND, et al. Processing emotional facial expressions influences performance on a Go/NoGo task in pediatric anxiety and depression. *Journal of Child Psychology and Psychiatry*. 2006; 47:1107–1115. [PubMed: 17076749]
- Ladouceur CD, Dahl RE, Williamson DE, Birmaher B, Ryan ND, Casey BJ. Altered emotional processing in pediatric anxiety, depression and comorbid anxiety-depression. *Journal of Abnormal Child Psychology*. 2005; 33:165–177. [PubMed: 15839495]
- Laje G, Paddock S, Manji H, Rush AJ, Wilson AF, Charney D, et al. Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. *American Journal of Psychiatry*. 2007; 164:1530–1538. [PubMed: 17898344]
- Lesch KP, Wolozin BL, Murphy DL, Reiderer P. Primary structure of the human platelet serotonin uptake site: Identity with the brain serotonin transporter. *Journal of Neurochemistry*. 1993; 60:2319–2322. [PubMed: 7684072]
- Levenson VV. Biomarkers: Diagnostic high-lights and surrogate end points. *Pharmacogenomics*. 2004; 5:459–461. [PubMed: 15212582]
- Lewinsohn PM, Rohde P, Seeley JR. Major depressive disorder in older adolescents: Prevalence, risk factors, and clinical implications. *Clinical Psychology Review*. 1998; 18:765–794. [PubMed: 9827321]
- Libby A, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. *American Journal of Psychiatry*. 2007; 164:884–891. [PubMed: 17541047]
- Majer M, Ising M, Kunzel HE, Binder EB, Holsboer F, Modell S, et al. Impaired divided attention predicts delayed response and risk to relapse in subjects with depressive disorders. *Psychological Medicine*. 2004; 34:1453–1463. [PubMed: 15724876]
- McClure EB, Adler A, Monk CS, Cameron J, Smith S, Nelson EE, et al. fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology*. 2007; 191:97–105. [PubMed: 16972100]
- Nelson EE, Leibenluft E, McClure EB, Pine DS. The social re-orientation of adolescence: A neuroscience perspective on the process and its relation to psychopathology. *Psychological Medicine*. 2005; 35:163–174. [PubMed: 15841674]
- Nock MK, Banaji MR. Prediction of suicide ideation and attempts among adolescents using a brief performance-based test. *Journal of Consulting Clinical Psychology*. 2007; 75:707–715. [PubMed: 17907852]
- O'Connor TG, Cameron JL. Translating research findings on early experience to prevention: Animal and human evidence on early attachment relationships. *American Journal of Preventive Medicine*. 2006; 31:175–181.
- Park RJ, Goodyer IM, Teasdale JD. Categorical overgeneral autobiographical memory in adolescents with major depressive disorder. *Psychological Medicine*. 2002; 32:267–276. [PubMed: 11866322]

- Park RJ, Goodyer IM, Teasdale JD. Effects of induced rumination and distraction on mood and overgeneral autobiographical memory in adolescent major depressive disorder and controls. *Journal of Child Psychology and Psychiatry*. 2004; 45:996–1006. [PubMed: 15225341]
- Perez-Edgar K, Fox NA, Cohn JF, Kovacs M. Behavioral and electrophysiological markers of selective attention in children of parents with a history of depression. *Biological Psychiatry*. 2006; 60:1131–1138. [PubMed: 16934774]
- Pine DS. Face-memory and emotion: Associations with major depression in children and adolescents. *Journal of Child Psychology and Psychiatry*. 2004; 45:1199–1208. [PubMed: 15335340]
- Resnick MD, Bearman PS, Blum RW, Bauman KE, Harris KM, Jones J, et al. Protecting adolescents from harm: Findings from the National Longitudinal Study on Adolescent Health. *Journal of the American Medical Association*. 1997; 278:823–832. [PubMed: 9293990]
- Roberson-Nay R, McClure EB, Monk CS, Nelson EE, Guyer AE, Fromm SJ, et al. Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: An fMRI Study. *Biological Psychiatry*. 2006; 60:966–973. [PubMed: 16603133]
- Rossello J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *Journal of Consulting Clinical Psychology*. 1999; 67:734–745. [PubMed: 10535240]
- Sallee FR, Vrindavanam NS, Deas-Nesmith D, Carson SW, Sethuraman G. Pulse intravenous clomipramine for depressed adolescents: Double-blind, controlled trial. *American Journal of Psychiatry*. 1997; 154:668–673. [PubMed: 9137123]
- Shaw DS, Schonberg M, Sherrill J, Huffman D, Lukon J, Obrosky D, et al. Responsivity to offspring's expression of emotion among childhood-onset depressed mothers. *Journal of Clinical Child and Adolescent Psychology*. 2006; 35:490–503. [PubMed: 17007595]
- Siegle GJ, Ghinassi F, Thase M. Neurobehavioral therapies in the 21st century: Summary of an emerging field and an extended example of cognitive control training for depression. *Cognitive Therapy Research*. 2007; 31:235–262.
- Silk J, Dahl RE, Ryan ND, Forbes EA, Axelson D, Birmaher B, et al. Pupillary reactivity to emotional information in child and adolescent depression links to clinical and ecological measures. *American Journal of Psychiatry*. 2007a; 164:1873–1880. [PubMed: 18056243]
- Silk J, Ziegler M, Whalen D, Dietz L, Dahl R, Birmaher B, et al. Expressed emotion in mothers of currently depressed, remitted, high-risk and low-risk youth: Links to child depression status and longitudinal course. *Journal of Clinical Child and Adolescent Psychiatry*. in press.
- Silk, JS.; Forbes, EE.; Whalen, DJ.; Bertocci, MA.; Prout, J.; Dahl, RE. Daily emotional and social experience in child and adolescent depression: An ecological momentary assessment study; Presented at the meeting of the Society for Research in Child Development; Boston, MA. 2007b; Mar.
- Silk JS, Shaw DS, Skuban EM, Oland AA, Kovacs M. Emotion regulation strategies in offspring of childhood-onset depressed mothers. *Journal of Child Psychology and Psychiatry*. 2006; 47:69–78. [PubMed: 16405643]
- Swartz HA, Frank E, Zuckoff A, Cyranowski JM, Cheng Y, Fleming MAD, et al. Brief interpersonal psychotherapy for depressed mothers whose children are receiving psychiatric treatment. *American Journal of Psychiatry*. in press.
- Thapar A, McGuffin P. Anxiety and depressive symptoms in childhood: A genetic study of comorbidity. *Journal of Child Psychology and Psychiatry*. 1997; 38:651–656. [PubMed: 9315975]
- The TADS Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. Treatment for Adolescent Depression Study (TADS) randomized controlled trial. *Journal of the American Medical Association*. 2004; 292:807–820. [PubMed: 15315995]
- The TADS Team. The Treatment for Adolescents with Depression Study (TADS): Long-term effectiveness and safety outcomes. *Archives of General Psychiatry*. 2007; 64:1132–1144. [PubMed: 17909125]
- Thomas KM, Drevets WC, Whalen PJ, Eccard CH, Dahl RE, Ryan ND, et al. Amygdala response to facial expressions in children and adults. *Biological Psychiatry*. 2001; 49:309–316. [PubMed: 11239901]

- Weersing VR, Brent DA. Cognitive behavioral therapy for depression in youth. *Child and Adolescent Psychiatric Clinics of North America*. 2006; 15:939–957. [PubMed: 16952769]
- Weissman MM, Pilowsky DJ, Wickramaratne PJ, Talati A, Wisniewski SR, Fava M, et al. Remissions in maternal depression and child psychopathology: A STAR\*D child report. *Journal of the American Medical Association*. 2006a; 295:1389–1398. [PubMed: 16551710]
- Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky DJ, Verdell H. Offspring of depressed parents: 20 years later. *American Journal of Psychiatry*. 2006b; 163:1001–1008. [PubMed: 16741200]
- Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: A meta-analysis. *Psychological Bulletin*. 2006; 132:132–149. [PubMed: 16435960]
- Wilkinson PO, Goodyer IM. Attention difficulties and mood-related ruminative response style in adolescents with unipolar depression. *Journal of Child Psychology and Psychiatry*. 2006; 47:1284–1291. [PubMed: 17176383]
- Young JF, Mufson L, Davies M. Impact of comorbid anxiety in an effectiveness study of interpersonal psychotherapy for depressed adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006; 45:904–912. [PubMed: 16865032]
- Zarate C, Singh J, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh D, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*. 2006; 63:856–864. [PubMed: 16894061]

### Key points

- Research on biological markers of depression should pursue both state-like endophenotypes and trait-like biomarkers, and conduct studies that distinguish between the two.
- Incorporate measures of neurocognitive status, reward orientation, positive and negative affect, and other biomarkers into future treatment research in order to elucidate mechanisms, personalize treatment, and frame future treatment targets
- While around 11 times more depressed youth will benefit from pharmacotherapy than will experience a suicidal event, outcomes for pharmacotherapy could be improved by dosing patients based on known developmental differences in drug metabolism, conducting dose-ranging studies, and developing interventions to improve adherence.
- Combination of CBT and antidepressant medication results in the most rapid and complete recovery, but consolidation of treatment response and prevention of relapse require longer-term continuation treatment.
- Identification and treatment of maternal depression can prevent the outcome of child disorder and improve treatment outcomes in youth in mental health care
- Depression is comorbid with many other health risk behaviors, such as overeating, having unprotected sex, low levels of physical activity, and substance abuse. Interventions that address the common causes of these difficulties should be developed and tested.