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Depressive Disorders (K Cullen, Section Editor)

Predictors of Treatment Outcome in Adolescent Depression

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Abstract

Purpose of review Major depressive disorder is a global public health concern that is common in adolescents. Targeting this illness at the early stages of development is critical and could lead to better long-term outcomes because the adolescent brain is highly plastic and, hence, neural systems are likely to be more malleable to interventions. Although a variety of treatments are available, there are currently no guidelines to inform clinicians which intervention might be most suitable for a given youth. Here, we discuss current knowledge of prognostic and prescriptive markers of treatment outcome in adolescent depression, highlight two major limitations of the extant literature, and suggest future directions for this important area of research.

Recent findings Despite significant effort, none of the potential demographic (gender, age, race), environmental (parental depression, family functioning), and clinical (severity of depression, comorbid diagnoses, suicidality, hopelessness) predictors have been robustly replicated to warrant implementation in clinical care. Studies on biomarkers that truly reflect pathophysiology are scarce and difficult to draw conclusions from.

Summary More efforts should be directed towards potential neurobiological predictors of treatment outcome. Moreover, rather than evaluating potential predictors in isolation, modern machine learning methods could be used to build models that combine information across a large array of features and predict treatment outcome for individual patients. These strategies hold promise for advancing personalized healthcare in adolescent depression, which remains a high clinical priority.

Introduction

Major depressive disorder (MDD) is a global public health concern that is common in adolescents [1]. Recent epidemiological data indicate a lifetime prevalence of ~ 11% in mid-to-late adolescence [2], and longitudinal studies suggest that this debilitating condition is chronic and highly recurrent [3, 4]. MDD affects psychosocial functioning in youths and is frequently associated with problems in social, emotional, and cognitive development [5]. Moreover, depression is a major risk factor for suicide in adolescents [6]—with an estimated 75% of youths who attempted suicide also meeting the diagnostic criteria for MDD [7]. Without appropriate treatment, adolescent depression could lead to continued impairments in physical and mental health throughout the lifespan [1]. Critically, this age group represents an important period of neural plasticity whereby different brain regions are still maturing at different rates. For example, subcortical areas tend to mature earlier in the typical adolescent brain; on the other hand, prefrontal cortical regions take longer to mature [8] and differences in rates of prefrontal maturation have been found to be associated with depressive and anxiety symptoms in children and adolescents [9]. Hence, targeting MDD at the early stages of development could lead to better long-term outcomes because the neural systems are likely to be more malleable to various interventions.

Clinical guidelines recommend psychotherapy, antidepressants, or a combination of both for the treatment of adolescent depression [10, 11]. However, findings from major multisite randomized controlled trials and meta-analyses revealed that at least 40% of depressed youths fail to exhibit adequate clinical response to these interventions [12–15]. These modest response rates have been attributed to the fact that MDD is highly heterogeneous with multiple etiologies and symptom profiles [16]. Hence, some patients may benefit more from a certain type of treatment while others might be better suited for other interventions. Identifying pretreatment variables that predict the likelihood of treatment response would thus have significant clinical value.

Markers of treatment outcome can be broadly divided into two classes. Prognostic variables are non-specific and predict outcome regardless of which intervention is selected. Hence, they are useful for detecting vulnerable patients who might be treatment-resistant and require a more intensive intervention with careful monitoring from the outset. In contrast, prescriptive markers indicate the likelihood of success for a specific intervention (e.g., psychotherapy vs. antidepressant medication). Thus, they could guide treatment choice within the clinic by providing information on which treatment might be most beneficial for a given patient [17].

In this article, we discuss current knowledge of prognostic and prescriptive markers of treatment outcome in adolescent depression, highlight limitations in the existing literature, and provide an overview of promising future directions for this important area of research.

Current knowledge of markers of treatment outcome

Demographic variables

Gender

Given that post-pubertal female youths are twice as likely to be affected by MDD than their male counterparts [18], gender has been considered as a potential marker of treatment outcome. However, studies evaluating antidepressants [19–22, 23•, 24], psychotherapy [19, 23•, 25–28], or a combination of both [19, 20, 22, 23•] have consistently found that gender is neither a prognostic nor prescriptive marker. An exception was Cheung et al. [29], who reported that being female increased the probability of MDD remission regardless of whether fluoxetine or placebo was administered.

Age

The prevalence of MDD is low in pre-pubertal children, but rates begin to increase in early teens and substantially throughout adolescence [1]. Since depression appears to be less deeply entrenched in younger youths, lower age might be expected to be associated with better treatment outcomes. In support of this, Curry and colleagues showed that age was a prognostic marker; specifically, younger adolescents reported lower depressive symptom severity after 12 weeks of treatment with fluoxetine, cognitive behavior therapy (CBT), or fluoxetine combined with CBT [19]. An early study also found that younger adolescents have higher rates of remission from CBT [26]. However, many other investigations utilizing antidepressants [20–22, 23•, 24, 29], psychotherapy [23•, 25, 27, 28], or a combination of both [20, 22, 23•] have failed to find a relationship between age and treatment outcome.

Race

The current literature strongly suggests that, among youth samples, race is not associated with treatment outcomes by antidepressants [19, 21, 22, 23•, 24, 29], psychotherapy [19, 23•, 26, 27], or both combined [19, 22, 23•]. One study reported that Caucasian youths derive more benefits from community psychotherapy than their minority counterparts, but this is likely confounded by therapy dose: 56% of minority youths attended fewer than 8 sessions of treatment, compared to only 17% for Caucasian adolescents [30]. Unfortunately, reasons for the poor follow-up in minority adolescents are unclear (e.g., might the therapy approach have been culturally insensitive or linked to specific barriers faced by minority families that had not been recognized or addressed?). Future investigations should address these possible sources, especially in light of evidence indicating disparities in mental healthcare for racial minority youths [31] as well as higher rates of suicide in Black (compared to White) adolescents [32].

Environmental variables

Parental depression

Even though the offspring of parents with a history of MDD are three to four times more likely to be depressed than those of healthy parents [33–35], several studies have reported that parental depression was not a prognostic or prescriptive marker of antidepressants [19, 23•], psychotherapy [19, 20, 23•, 28], or a combination of both [19, 23•]. Tao and coworkers, however, found that positive first-degree family history of depression was associated with greater likelihood of remission after 12 weeks of open-label fluoxetine treatment; however, the investigators conceded that the study clinicians might have been positively biased towards estimating improvements and the assessment of treatment outcome would be more accurate with independent evaluators [21].

Family functioning

Higher levels of conflict in the family have been associated with the vulnerability and severity of depression in adolescents [36, 37]. Conversely, more cohesive

and supportive family environments are thought to promote resiliency for depressed youths and, thus, might be expected to predict better treatment outcome [27]. The extant literature, albeit modest, seems to support this notion, suggesting that healthier family functioning is a positive prognostic indicator across a variety of interventions [38–40], including antidepressants [22, 41], psychotherapy [27, 41–43], or both combined [22, 41] (but see [19, 28] for null findings).

Clinical variables

Severity of depression

Greater MDD severity indicates a more pernicious form of the disorder and, thus, might be postulated as a general predictor of poorer treatment outcome. In support of this, trials with antidepressants [20, 22], psychotherapy [25, 26, 28, 42, 44], or both [20, 22] have found that lower levels of depression at baseline were associated with better prognosis after treatment. Some studies, however, have found no relationship between baseline severity and outcome to treatment [21, 24, 27, 29].

Interestingly, two studies that analyzed data from the large Treatment for Adolescents with Depression Study (TADS) found evidence for initial MDD severity as a prescriptive (rather than prognostic) marker—albeit with different conclusions [19, 23•]. Curry et al. reported that mildly and moderately depressed adolescents benefitted more from fluoxetine plus CBT than either option alone, whereas there was no advantage in combined treatment for severely depressed youths [19]. In contrast, Gunlicks-Stoessel and colleagues showed that higher levels of MDD at baseline were associated with poorer outcomes when treated with CBT, but not fluoxetine or a combination of both [23•]. This discrepancy might have arisen because participants randomized to the placebo condition of TADS were included for analysis in the former [19] but not latter [23•] study.

Comorbid diagnoses

Although comorbid conditions such as generalized anxiety disorder and attention-deficit/hyperactivity disorder (ADHD) are highly common in adolescent depression [12], research examining the impact of co-occurring diagnoses and treatment outcome have yielded mixed results. In studies of psychotherapy, a number of investigators have found no association between co-occurring conditions and treatment outcome [25, 26, 30, 45, 46], but others have reported that depressed youths with any comorbid condition were less likely to experience benefits [28, 47]. Similarly, some treatment trials with antidepressants or antidepressants plus psychotherapy have found that the presence of comorbid disorders is a prognostic marker of worse outcomes [19, 20, 29], while findings from other studies suggest comorbidity did not impact treatment response [21, 23•, 24]. One study also reported that the presence of more comorbid disorders is a prescriptive marker of better outcome to treatment by CBT plus medication (SSRI or SNRI) compared to medication alone [22].

Suicidality and hopelessness

Feeling of hopelessness, as well as suicide ideation and attempts, might reduce a depressed youth's willingness to participate in treatments and ability to benefit from the intervention, particularly those that are psychosocial in nature. In line with this, suicidality and/or hopelessness has emerged as a prognostic marker of poorer outcomes in studies of psychotherapy [19, 27, 28, 48], antidepressants [19, 20, 22], and a combination of both [19, 20, 22]. Barbe and colleagues also found that lifetime suicidality is a prescriptive marker of outcome to different psychotherapy treatments [49]. Specifically, depressed adolescents with suicidal history respond less favorably to non-directive supportive therapy whereas suicidality did not moderate response for CBT and systemic-behavioral family therapy. Nevertheless, some studies have reported no impact of suicidality on outcome across a variety of interventions [21, 23•, 25].

Biological variables

Few studies have investigated potential biological markers of treatment outcome. In a small open trial with 13 adolescents, Forbes and coworkers reported that greater baseline striatal reactivity to reward was associated with worse depression after 8 weeks of CBT or CBT plus SSRI [50•]. Interestingly, a recent study in 36 teenage girls with MDD found the opposite; greater pretreatment reward responsiveness, as assessed by late positive potential (LPP) to rewards, predicted greater improvement in depressive symptoms after a 12-week course of CBT [51]. Similarly, Barch and colleagues recently reported that higher pretreatment levels of LPP to positive pictures was associated with higher odds of remission from young depressed children (aged 4.0–6.9 years old) after 18 weeks of Parent-Child Interaction Therapy-Emotion Development (PCIT) [52]. Additional research is required to investigate whether some inconsistencies might stem at least partly from differences in sample (girls only [51] vs. both genders [50•]), diagnoses (77% [50•] vs. 33% with comorbid generalized anxiety disorder [51]), age/development (young children [52] vs. older youths [50•]), type of psychotherapy treatment (CBT [50•] vs. PCIT [52]), and differences between reward processing tasks. Clarifying this discrepancy could provide important insights on the mechanisms of psychotherapy response.

An exploratory study also found that (1) greater baseline amygdala resting-state functional connectivity (rsFC) with the right central parietal-opercular cortex and Heschl's gyrus, (2) lower amygdala rsFC with the right precentral gyrus and left supplementary motor area, as well as (3) greater activation of the bilateral anterior cingulate cortex and left medial frontal gyrus during an emotion task predicted better response to an 8-week course of SSRIs [53•]. However, these findings are highly tentative as the sample size was small (N = 13), and treatment was not controlled (i.e., type and dose of medication were unknown and some individuals could be receiving additional psychotherapy support). Finally, Goodyer et al. reported that higher evening ratio of cortisol-to-dehydroepiandrosterone in youths at study entry predicted persistent MDD diagnoses after 36 weeks, but this finding should be interpreted with caution as treatment during the follow-up period was not systematically assessed and controlled [54].

Interim summary

Age, gender, race, and history of parental depression do not appear to have any impact on treatment efficacy. In contrast, existing studies seem to suggest that worse family functioning, higher baseline levels of depression, presence of comorbid diagnoses, as well as suicidality and hopelessness might be negative prognostic markers of treatment outcome—although findings are mixed. These factors are likely to be interrelated and might indicate a more pernicious form of MDD that might require a more intensive intervention coupled with careful monitoring. Finally, research on biological markers of treatment outcome in adolescent depression is scarce and currently insufficient to draw any conclusions.

Limitations and future directions

Despite significant efforts to predict treatment outcome in adolescent MDD, reliable prognostic or prescriptive markers have not emerged. We next highlight two major limitations in the current literature and provide suggestions for tackling them as future directions in this important field.

Problem with evaluating potential predictors in isolation

A number of prior studies have examined the potential predictive ability of candidate variables in isolation and adopted a liberal approach that did not correct for multiple comparisons (e.g., [19, 20, 24–28, 41]). This might increase the chances of committing a type 1 error; this is incorrectly rejecting a null hypothesis when it is true. Moreover, given the complex etiology, course, and clinical expression of MDD, any single factor is likely to explain only a very small amount of outcome variance.

To overcome these limitations, multivariate machine learning approaches can be used to build models that combine information across a large collection of features and predict treatment outcome for individual patients. The examination of all potential predictors in an unbiased, data-driven manner affords the opportunity to discover novel markers, which might not have been previously identified based on clinical perceptions of what is likely to influence treatment. To date, only one study has attempted this approach in adolescent MDD. Gunlicks-Stoessel and colleagues adopted the Generalized Local Learning algorithm to investigate 182 baseline variables in 282 depressed patients from the TADS clinical trial and identified a model that could differentially predict response to fluoxetine, CBT, and CBT plus fluoxetine [23•]. Importantly, the model had been internally validated with a leave-one-out procedure, suggesting that performance was not grossly influenced by particular individuals in the training data. Nevertheless, these promising findings will need to be externally validated in an independent sample of unseen cases in order to assess true generalizability [55].

An important caveat that should be noted when applying data-driven machine learning is sample size. Although algorithms such as elastic net regression and tree-based ensembles will converge in small samples with many variables (even in situations when number of predictors exceed number of cases), it is crucial to (1) collect sufficient data in order to derive stable predictions and (2)

validate performance of the models in independent samples in order to produce generalizable predictions. Relatedly, Luedtke et al. recently conducted a simulation study to estimate the sample size needed to detect treatment effects large enough to be clinically significant. They concluded that at least 300 patients are required for each treatment group [56]—which is substantially larger than most published studies. One possible way to overcome this might be to conduct meta-analyses that aggregate data across studies, provided there is adequate overlap in terms of participant characteristics, potential predictors, and outcome variables (such as in [57]).

Neural predictors of treatment outcome

Advances in multimodal neuroimaging techniques have helped to identify neurobiological markers reflecting underlying pathophysiological processes in depression [58]. Consequently, numerous studies have been conducted—in depressed adults—to investigate the extent to which these biomarkers can serve as predictors of treatment outcome (e.g., see reviews by [59–64]). Surprisingly, existing research in the adolescent literature has almost exclusively focused on identifying potential predictors from demographic, environmental, and clinical characteristics; and studies investigating biomarkers are scarce.

Based on emerging evidence suggesting that altered reward capacity might be a key contributing factor to the development of depression [65], two previous studies focused on neural markers of reward as predictors of CBT response (albeit with opposite results) [50•, 51]. However, it remains unknown whether objective markers of reward capacity might also predict outcome to antidepressant drugs in depressed adolescents. Recent studies in adults with MDD have found that better pretreatment reward processing (as assessed behaviorally as well as neurally) was associated with superior response to dopaminergic, but not serotonergic-based, medications, suggesting that baseline reward capacity might potentially be a useful prescriptive marker of antidepressant drugs [66, 67]. Given that subcortical regions mature earlier in the typical adolescent brain while prefrontal cortical structures mature later [8], it will be interesting to examine whether similar neural mechanisms might exist in depressed youths and predict differential effectiveness to various classes of antidepressants.

Another promising biological marker of treatment outcome that has emerged from research in adults with MDD is pretreatment activity within the rostral anterior cingulate cortex (rACC). Greater baseline rACC activity reliably predicts positive outcome across a variety of treatments (e.g., different classes of antidepressant drugs, sleep deprivation, placebo, and brain stimulation), with a meta-analysis reporting that this effect has been replicated across 19 studies with a large effect size of 0.918 [68]. A large multisite clinical trial of 248 depressed adults randomized to sertraline and placebo recently further extended this finding by providing evidence for the incremental predictive ability of the rACC marker; that is, pretreatment activity in the rACC predicted symptom improvement even after controlling for demographic and clinical variables (e.g., age, sex, race, and severity of depression) thought to be linked to treatment outcome [69]. Hence, the rACC is now considered to be one of the most robust prognostic markers of treatment in adult MDD.

Significant evidence indicates that healthy development of the ACC is crucial for supporting adaptive affect and behavioral regulation from adolescence through adulthood; and dysfunctions in this region are strongly implicated in the pathogenesis of adolescent MDD [70, 71]. Collectively, these considerations suggest that biomarkers of ACC function might be important in predicting treatment outcome in depressed youths. An exciting study by Klimes-Dougan and coworkers has provided initial evidence to support this, showing that higher baseline levels of ACC (including rACC) activation in response to negative emotion predicted greater improvement in depressive symptoms after 8 weeks of SSRI treatment [53•]. While these findings suggest consistency across development, it should be noted that their sample size was small (N = 13) and additional studies will be needed to ascertain the predictive ability of the rACC activation across treatment modalities in adolescents.

Conclusion

Adolescence represents a highly vulnerable period for the onset of depression. It is important to target MDD in the early stages of development because the adolescent brain is highly plastic and neural systems are more likely to be malleable to interventions, which could lead to better long-term outcomes. Although a variety of treatments are available for adolescent depression, there are currently no guidelines to inform clinicians which intervention might be most suitable for a given youth. Much research has been conducted to identify potential demographic, environmental, and clinical predictors, but none has been robustly replicated to warrant implementation in clinical care. In contrast, studies on biomarkers that truly reflect pathophysiology are scarce and only just beginning. Increasing focus on potential neurobiological predictors of treatment outcome, in combination with modern machine learning methods, will have important implications for advancing personalized healthcare for adolescents suffering from depression.

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Compliance with ethical standards

Conflict of interest

Over the past 3 years, Dr. Diego Pizzagalli has received consulting fees from BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Engrail Therapeutics, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals as well as one honorarium from Alkermes. In addition, he has received stock options from BlackThorn Therapeutics and research support from National Institute of Mental Health, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. Dr. Ang declares that he has no conflict of interest.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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