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Anhedonia Predicts Poorer Recovery among Youth with Selective Serotonin Reuptake Inhibitor-Treatment Resistant Depression

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Abstract

Objective—To identify symptom dimensions of depression that predict recovery among SSRI-treatment resistant adolescents undergoing second-step treatment.

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Method—The Treatment of Resistant Depression in Adolescents (TORDIA) trial included 334 SSRI-treatment resistant youth randomized to a medication switch, or a medication switch plus CBT. This study examined five established symptom dimensions (Child Depression Rating Scale-Revised) at baseline as they predicted recovery over 24 weeks of acute and continuation treatment. The two indices of recovery that were evaluated were time to remission and number of depression-free days.

Results—Multivariate analyses examining all five depression symptom dimensions simultaneously indicated that Anhedonia was the only dimension to predict a longer time to remission, and also the only dimension to predict fewer depression-free days. In addition, when Anhedonia and CDRS-total score were evaluated simultaneously, Anhedonia continued to uniquely predict longer time to remission and fewer depression-free days.

Conclusions—Anhedonia may represent an important negative prognostic indicator among treatment resistant depressed adolescents. Further research is needed to elucidate neurobehavioral underpinnings of anhedonia, and to test treatments that target anhedonia in the context of overall treatment of depression.

Keywords

depression; adolescence; treatment-resistant; cognitive-behavioral therapy; clinical trial

Introduction

Despite advances in treatments for adolescent depression in recent years, approximately 30–50% of youth remain nonresponsive to leading first-step treatments including SSRI treatment, cognitive behavioral treatment (CBT), or combination treatment (SSRI and CBT).[1] Among youth who do respond, up to 50% exhibit residual symptoms.[2] In response to the high rate of non-response, the Treatment of Resistant Depression in Adolescents (TORDIA) examined the effects of a second-step treatment for youth who were resistant to a first-step SSRI treatment. Second-step randomized treatments included: 1) switch to a different SSRI; 2) switch to a different SSRI plus CBT; 3) switch to venlafaxine, or 4) switch to venlafaxine plus CBT. The results of the trial are reported in detail elsewhere,[3] but one major conclusion was that a switch to a different antidepressant can be beneficial for youth who were resistant to a first round of SSRI treatment, and that a combination of CBT and medication switch may yield a higher response rate than a medication switch alone. Yet, even among the highest response group in TORDIA, the rate of clinical response was only 54.8% following acute treatment. Remission rates in TORDIA were 40% by the end of 24 weeks,[4] and 61.1% at 72-week follow-up,[5] consistent with other large trials of youth depression treatment.[6] This general pattern of incomplete benefit highlights the need to optimize treatment approaches.

An important finding in the treatment of adolescent depression is that the likelihood of remission is evident early in the course of treatment. In the TORDIA trial, remitters and non-remitters showed a diverging trajectory of symptoms by 6 weeks, with a rate of symptom resolution among remitters that was nearly twice that of non-remitters.[4] By 12 weeks, treatment response predicted a 3-fold higher likelihood of eventual remission. Based on these and other findings,[7] Emslie et al.,[4] call for “early and vigorous intervention” to accelerate a positive trajectory of symptom relief, and to increase the likelihood of long-term recovery.

Personalizing treatment approaches to individual baseline characteristics may improve recovery among youth with unremitting depression.[8] To this end, Asarnow et al.[9] examined predictors of treatment response in the TORDIA trial. Much in line with first-step treatment

trials[10–14] predictors of response included depression severity, hopelessness, suicidal ideation, youth reported family conflict, and functional impairment. Additionally, moderators of treatment response indicated that CBT plus medication is perhaps optimal for youth with depression comorbid with other disorders, particularly anxiety and ADHD. However, depression is a heterogeneous disorder, and examining how unique symptom dimensions of depression relate to recovery may also reveal avenues for personalized treatment. Treatment-resistant youth may commonly exhibit depression symptom dimensions that are not adequately resolved by existing approaches. Knowledge of these dimensions can inform clinical prognosis, and guide interventions that explicitly target key symptom dimensions and neurobehavioral underpinnings.[15]

To identify which depression symptom dimensions to target as a means to speed and improve recovery, it is important to examine the time course of symptom resolution, rather than collapsing data categorically (e.g., remitted versus unremitted) based on single-end point scores. Some youth may have a dramatic and immediate response to treatment, while others may respond more slowly, or not at all. It is possible that such temporal patterns of treatment response relate to presenting depression symptom dimensions in predictable ways that could impact clinical decision making. For example, if somatic symptoms are reliably associated with a longer time to remission, future research may use existing or novel treatment approaches to target key disruptions more explicitly at the start of treatment (e.g. sleep intervention), and subsequently evaluate whether or not these approaches can speed recovery and bring more youth to full remission status.

In this study, we examined how depression symptom dimensions in participants in the TORDIA study with SSRI-resistant depression relate to time to remission over the course of 12 weeks of acute second-step treatment, and 12 weeks of continuation treatment. As a secondary index of recovery, we also examined how depression symptom dimensions relate to depression-free days over the 24 week period. Our broad aims were to identify depression symptom dimensions that may serve as unique prognostic indicators, and to consider how relations between symptom dimensions and recovery may signal opportunities for targeted treatments that could speed recovery and improve rates of remission. Although we anticipated that one or more depression symptom dimensions would uniquely predict time to remission and number of depression-free days, we did not make *a priori* predictions about specific dimensions given limited literature to guide hypothesis generation.

Method

Overview

A brief description of method, study design and sample as relevant to the current study is presented below, and further details are provided elsewhere.[3] The study was approved by internal review boards local to the 6 research sites. All participants gave informed consent/assent (as appropriate), and parents gave informed consent.

Participants

Participants were 334 adolescents aged 12 to 18 years who were in active treatment with an SSRI for major depressive disorder (by DSM-IV criteria), and evidenced clinically significant depression by a Children's Depression Rating Scale/Revised (CDRS-R) total score of 40 or higher, and a Clinical Global Impression/Severity subscale of 4 or higher (moderate or high severity). Prior to entry into the study, participants had undergone an SSRI regimen for at least 8 weeks, the last 4 of which were at a dosage of at least 40 mg per day of fluoxetine or its equivalent (e.g., 40 mg paroxetine, 40 mg citalopram, 20 mg s-citalopram, or 150 mg sertraline). We also included participants who, after attempting a

dosage comparable to 40 mg of fluoxetine, could only tolerate a dose that was the equivalent of 20mg of fluoxetine for at least 4 weeks (19/334 participants; 5.7%). Exclusion criteria included 2 or more previous adequate SSRI trials; previous non-response to venlafaxine (4 weeks at a dose of 150 mg); previous CBT trial with more than 6 sessions; on medications with psychoactive properties, with the exception of some study-allowed medications including stable doses (≥12 weeks) of stimulants, hypnotics (trazodone, zolpidem, zaleplon), or antianxiety agents (clonazepam, lorazepam); diagnoses of bipolar I or II, psychosis, autism, eating disorders, alcohol or drug abuse or dependence, and hypertension; and female subjects who were pregnant, breastfeeding, or not reliably using contraception. We did not exclude those who used alcohol or substances and did not meet criteria for abuse or dependence (see Goldstein et al.[16] for more details). Eleven participants who were offered enrollment declined participation.

The sample had a mean age of 16 years (SD 1.6 years), 70% were female, and 84% were white (5% Hispanic/Latino, 5% biracial, 3% black, 2% Asian, and 2% other). The median annual family income was $61,000 (SD=$55,823). The subjects had moderately severe and chronic depression (mean CDRS-R=59, SD=10; 56% duration of 2 years or longer). Co-occurring diagnoses were observed in 51.7% of the youths, including anxiety disorders (38.9%), conduct or oppositional disorders (9.6%), and ADHD (16.6%)–some youth had more than one co-occurring condition. Duration of pre-study treatment was a median of 17 weeks for SSRI treatment, and a median of 8 psychotherapy sessions in the previous 12 weeks.

Study Design

Consented participants entered the study for a first assessment, continued on their pre-study medication regimen for another 2 weeks, and were reassessed. At the second baseline assessment, youth exhibiting continuing high levels of depressive symptoms (CDRS-R > 40, and decrease in CDRS-R scores of 30% or less from assessments 1 to 2) were randomized to treatment condition.

Treatments

Participants were randomized to receive a different SSRI or venlafaxine, with or without CBT, for 12 weeks of acute treatment followed by 12 weeks of continuation treatment. CBT included 12 weekly sessions followed by up to 6 booster sessions over the subsequent 12 weeks, using techniques of behavior activation, cognitive restructuring, problem-solving, social skills training, and emotion regulation. Medication was administered under double-blind conditions for the first 12 weeks, after which responders continued blinded treatment and non responders entered clinically indicated open-label treatment, which could consist of a higher medication dose, a switch to another medication, augmentation with another medication, CBT, or other psychotherapy.

Assessments—To assess diagnostic status, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL)[17] was administered at study entry. Inter-rater reliability for depression and dysthymia diagnoses was high: kappa=0.70, 95% CI: 0.49–0.89, N=150.

Severity of depression symptoms (the primary outcome variable) were determined by independent evaluator (IE) ratings of depressive symptoms on the Child Depression Rating Scale-Revised (CDRS-R, range 17–113) at baseline, 6, and 12 weeks. CDRS-R is a semi-structured interview that assesses symptom severity with possible scores ranging from 1–7. Inter-rater reliability was high: CDRS-R, intraclass correlation = 0.85; 95% confidence interval (CI) 0.80–0.89, N= 324.

To determine remission status, at week 24 the IE rated the week-by-week severity of depressive disorder for the previous 3-month period using the Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE), using a 4-point scale (1=not present, 2=possible, 3=probably, 4=definite). Remission was defined as at least three consecutive weeks without clinically significant depressive symptoms.[18]

Depression-free days have been deemed to be a valid and clinically-relevant measure for examining treatment outcomes that reflect the course of symptom change over time because they estimate the duration of time spent in various stages of remission, as well as the cycling between remission and relapse that is so common to depression.[19–21] To calculate depression-free days, CDRS-R scores were used at four assessment points (baseline, week 6, week 12, and week 24). For assessment periods when scores exceeded accepted clinical cutoff points for remission,[2] each day within the assessment period was assigned a "0" to reflect a depression-free day. For assessment scores of 45 or greater, all days within the assessment period were coded as a "1" to reflect that they were not free of depression. Finally, for assessments within the range of 29–45, each day within the assessment period was assigned an interpolated value. The interpolated value used quadratic weighting between the non-depressed and fully depressed thresholds to estimate a value for each day in the interval. The number of depression-free days was calculated as the number of days in the study minus days with significant depression symptoms.

Data analysis

We calculated a sum of items for each of five symptom dimensions from the CDRS-R.[22] These dimensions (see Table 1) included Reported Depressed Mood (Irritability, Self Esteem, Depressed Mood, Weeping), Anhedonia (Social Withdrawal, Difficulty Having Fun), Somatic Symptoms (School Work, Sleep, Appetite, Fatigue, Physical Complaints), Morbid Thoughts (Guilt, Morbid Ideation, Suicidal Ideation), and Observed Depression (Depressed Affect, Speech, Hypoactivity). The symptom dimensions were then used to predict time to remission or depression-free days through the continuation phase of treatment (i.e., 24 weeks). Cox Proportional Hazards were used to predict time to remission, and linear regression models were used to predict depression-free days. We first estimated univariate models including one CDRS-R dimension at a time to predict time to remission or depression-free days after controlling for adolescent age, sex, and race (coded as Caucasian vs. non-Caucasian). Next, we estimated multivariate models that included all five CDRS-R dimensions simultaneously, along with adolescent age, sex, and race, to predict time to remission or depression-free days.

Results

Baseline dimension scores and remission through continuation treatment

Through 24 weeks, 130 (38.9%) youth achieved remission. For univariate models, higher levels of Reported Depressed Mood, Anhedonia, and Somatic Symptoms, but not Morbid Thoughts or Observed Depression, predicted a longer time until remission (Table 2). In the multivariate model, only higher levels of Anhedonia continued to predict a longer time until remission (Table 2).

Baseline dimension scores and number of depression-free days through continuation treatment

In the univariate models, all depression symptom dimensions were significant predictors of a fewer number of depression-free days (Table 3). In the multivariate model, only a higher level of Anhedonia was associated with a fewer number of depression-free days.

Post-hoc analyses—As a way of comparing the added utility of the Anhedonia symptom dimension relative to the CDRS-R total score, we estimated additional models that included both CDRS-R total score and Anhedonia to predict time to remission and depression-free days through week 24 when controlling for child age, sex and race. Only Anhedonia significantly predicted time until remission (Anhedonia: *HR = .90*, *95% CI =* .83–.97, $p < .01$; CDRS-R total score: *HR = .*99, *95% CI =* .97–1.01, $p = .30$), such that higher Anhedonia was associated with longer time until remission. For the model predicting depression-free days, both Anhedonia and the total score were significant predictors of number of days well ($B = -3.16$, $SE = 1.16$, $p < .01$, $pr = -.16$; $B = -.96$, $SE = .29$, $p < .01$, $pr = -.20$, respectively).

To address the possibility that differences in the ranges and variances of CDRS-R dimensions biased results, multivariate survival analyses for time to remission through week 24 and regression analyses for number of depression-free days were repeated using standardized CDRS-R dimension scores, whereby the mean of each dimension was zero with a standard deviation of one. Conclusions from these analyses are identical to those from using raw dimension scores.

Lastly, we examined the role of CBT treatment as a moderator between specific dimensions and recovery. We estimated a final model including main effects for each CDRS-R dimension, whether the individual received CBT, and interaction terms for CBT X Symptom Dimension (for each dimension). No significant interactions between CBT and dimensions were found.

Discussion

This study examined how symptom dimensions of depression may predict indices of recovery among SSRI-resistant adolescents enrolled in second-step treatment as part of the TORDIA trial. Anhedonia emerged as a key dimension predicting recovery. Anhedonia predicted a longer time to remission when all five symptom dimensions of depression were included simultaneously in a predictive model. Moreover, Anhedonia continued to predict time to remission when examined simultaneous to total CDRS-R score. As the confidence intervals for the association between Anhedonia and remission, and between the CDRS-R total score and remission are non-overlapping, this suggests that the effect for Anhedonia is stronger than that for the total score in predicting time to remission. Analyses examining depression-free days revealed similar outcomes. Taken together, these data suggest that Anhedonia robustly predicts both time to remission and depression-free days above and beyond other symptoms dimensions of depression; and above and beyond total CDRS-R score.

Anhedonic symptoms may serve as an important prognostic tool for identifying youth who may be at risk for a poorer or delayed recovery. Also, these data suggest that anhedonia may be blocking or slowing remission and could represent an important target for intervention. It is also possible that anhedonic symptoms reflect a marker of severity such that these are among the last symptoms to remit, though the likelihood of this is reduced by results demonstrating that Anhedonia predicted recovery above and beyond CDRS-total score at baseline. Identifying anhedonic symptoms in depressed youth early in treatment may provide opportunities to monitor symptoms more closely and intervene more aggressively to improve outcomes. Anhedonic symptoms have been shown to be associated with underlying positive affective systems (positive emotion, appetitive motivation, and features of reward-related circuitry);[23] and although positive and negative affective systems certainly interact, they also carry unique functions[24] and are not simply reciprocally activating.[25,26] As such, the centrality of anhedonia to recovery among treatment resistant youth, combined with

evidence that systems underlying anhedonia are functionally unique, suggests that targeting anhedonic symptoms and features of underlying positive affective systems carries potential to yield unique benefit.

No interaction effects between depression symptom dimensions and CBT treatment raises the question of whether or not existing CBT approaches adequately address anhedonic symptoms. In a previous component analysis of the CBT delivered in TORDIA, the most commonly used interventions were mood monitoring and cognitive restructuring.[27] Behavior activation (BA)—an approach that may more directly target anhedonic symptoms in part by increasing exposure to and reinforcement from pleasant events—was also used, but only on average 1.5 times during the course of treatment. Thus, the treatment focused more on negative affect and cognitive distortions, with relatively less emphasis on increasing positively reinforcing experiences and related pleasure. An important set of questions for future research is whether CBT treatment that is augmented or front-loaded with BA approaches (or another intervention targeting anhedonia) for youth presenting with anhedonic symptoms may help to promote a more positive and rapid trajectory of recovery, and help youth to reach a full remission status.

Future research can capitalize on advances in the field of affective neuroscience and help to refine our understanding of these results. First, clinical trials that include neuroimaging and behavioral assessments of positive emotional and motivational functioning can help to determine if targeting anhedonia can uniquely alter underlying positive affective systems, and play a distinct role in improving remission rates and recovery among youth with treatment resistant depression. Second, there may be opportunities for novel treatment development that is informed by progress in affective neuroscience revealing a deeper understanding of positive affective systems and their neural underpinnings (e.g. fronto-striatal reward-related circuitry). For example, there are growing insights into how positive affective systems change and develop during the adolescent period,[28] as well as how these systems uniquely relate to the developmental pathophysiology[29–31] and clinical course of depression.[32–35] Importantly, positive affective systems and how they relate to clinical manifestations of anhedonia are likely complex. As one of several examples, basic science across both animal and human models elucidates distinctions between appetitive motivations (“wanting”) and consummatory pleasure (“liking”), which both fall under the broader construct of positive affect and reward-related circuitry.[36] Distinctions like these may inform our understanding of anhedonic symptom presentations (e.g. motivational anhedonia vs. consummatory anhedonia) and underlying neurobiology; as well as the use of existing interventions (e.g. BA), and the potential for complementary approaches that target these and other key deficits to alter underlying developmental pathways of depression.

Limitations to the study included that the continuation treatment (weeks 12–24) was not controlled, such that depression symptom dimensions may have been related to intervening variables that impacted time to remission or depression-free days. Second, the ethnic diversity of the sample was limited, which restricts generalizability of these findings.[3,9] Third, although we did examine how these findings interacted with medication versus combination treatment (medication plus CBT), a high percentage of youth were enrolled in open treatment from weeks 12 through 24 during which they may have received any treatment. As such, future research may benefit from a more controlled approach to the question of whether combination treatment is indicated for youth presenting with anhedonic symptoms. Also, while outside of the scope of the current study, it may be useful to further unpack these findings with attention to specific treatment strategies to ascertain whether treatment may be optimized by matching strategies to symptom dimensions (e.g. BA for youth with anhedonic symptoms). Finally, global measures of outcome such as those used in

this study may preclude detection of several possible pathways that can result in the same final net score of symptoms.

Despite these limitations, this was the first large-scale clinical trial among youth who were resistant to SSRI treatment, and it offers important insights into severely depressed adolescents. Other strengths include multiple assessments of symptoms over a longitudinal time-course, and the use of multiple indices of recovery. This allowed us to capture important temporal features that can be overlooked by the use of single end-point categories of remission/non-remission.

Overall, anhedonia is worthy of consideration as a prognostic feature and specific treatment target among youth with treatment-resistant depression. When considered from the framework of affective neuroscience, understanding anhedonia as it relates to developmental pathways of underlying positive affect systems and reward-related circuitry may provide opportunities for treatment innovation.

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Table 1

Inter-correlations and descriptive information for Child Depression Rating Scale-Revised factors at Baseline.

	Reported Depressed Mood	Anhedonia	Somatic Symptoms	Morbid Thoughts	Observed Depression	Baseline M (SD)	Range
Reported Depressed Mood		.35***	.36***	.37***	.05	17.48 (4.19)	6–28
Anhedonia			.17**	.08	.16**	8.03 (2.61)	2–14
Somatic Symptoms				.08	.03	19.23 (4.13)	6–30
Morbid Thoughts					.03	6.97 (3.52)	3–19
Observed Depression						6.93 (3.01)	3–18

Note: Correlations represent associations between factors at baseline.

** $p < .01$;

*** $p < .001$.

Table 2

Baseline Child Depression Rating Scale-Revised (CDRS-R) Dimensions and Time to Remission Through 24 Weeks

	Univariate Model[a] HR (95% CI)	Multivariate Model[b] HR (95% CI)
Reported Depressed Mood	.94 (.90–.99) *	.96 (.91–1.02)
Anhedonia	.88 (.82–.94) ***	.91 (.84–.99) *
Somatic Symptoms	.96 (.92–.99) *	.97 (.92–1.02)
Morbid Thoughts	.99 (.94–1.04)	.99 (.93–1.05)
Observed Depression	1.01 (.95–1.07)	1.05 (.98–1.12)

Note:

[a] Models are adjusted for child age, sex, and race (coded as Caucasian vs. non-Caucasian).

[b] The multivariate model includes all CDRS-dimensions simultaneously and is adjusted for covariates in the Univariate model.

* $p < .05$;

*** $p < .001$.

Table 3

Baseline Child Depression Rating Scale-Revised (CDRS-R) Dimensions and Number of Depression-free days Through 24 Weeks

	Univariate Model[a]		Multivariate Model[b]	
	B (SE)	**partial correlation (*pr*)**	**B (SE)**	**partial correlation (*pr*)**
Reported Depressed Mood	−2.63 (.65)***	−.23	−1.19 (.83)	−.09
Anhedonia	−5.21 (1.01)***	−.29	−4.355 (1.18)***	−.23
Somatic Symptoms	−1.92 (.67)**	−.17	−.89 (.71)	−.08
Morbid Thoughts	−2.04 (.74)**	−.16	−1.414 (.84)	−.11
Observed Depression	−2.08 (.94)*	−.13	−.84 (.96)	−.05

Note:

[a]Models are adjusted for child age, sex, and race (coded as Caucasian vs. non-Caucasian).

[b]The multivariate model includes all CDRS-dimensions simultaneously and is adjusted for demographic covariates in the Univariate model.

*$p < .05$;

**$p < .01$,

***$p < .001$.