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Effect of Two Psychotherapies on Depression and Disease Activity in Pediatric Crohn's disease

Eva Szigethy, M.D., Ph.D.¹, Ada O Youk, Ph.D.², Joseph Gonzalez-Heydrich, M.D.³, Simona I. Bujoreanu, Ph.D.³, John Weisz, Ph.D.⁴, Diane Fairclough, DPh⁵, Ducharme Peter, MSW³, Neil Jones, Ph.D.¹, Francis Lotrich, M.D., Ph.D.¹, David Keljo, M.D.⁶, Arvind Srinath, M.D.⁶, Athos Bousvaros, M.D.⁷, David Kupfer, M.D.¹, and David R. DeMaso, M.D.³

¹Department of Psychiatry, University of Pittsburgh School of Medicine

²Department of Biostatistics, University of Pittsburgh

³ Department of Psychiatry, Boston Children's Hospital

⁴Department of Psychology, Harvard University

⁵Department of Biostatistics and Informatics, Colorado School of Public Health

⁶Department of Pediatric Gastroenterology, Children's Hospital of UPMC

⁷Department of Pediatric Gastroenterology, Boston Children's Hospital

Abstract

Background—Crohn's disease (CD) is associated with depression. It is unclear if psychosocial interventions offer benefit for depressive symptoms during active CD. In this secondary analysis of a larger study of treating depression in pediatric IBD, we assessed whether cognitive behavioral therapy (CBT) would differentiate from supportive non-directive therapy (SNDT) in treating depression and disease activity in youth with CD. We also explored if somatic depressive symptoms showed a different pattern of response in the overall sample and the subset with active IBD.

Methods—Youth with depression and CD (n=161) were randomized to 3-months of CBT (teaching coping skills) or SNDT (supportive listening). Depressive severity was measured using the Children's Depression Rating Scale-Revised (CDRS-R) with the somatic depressive subtype consisting of those CDRS-R items which significantly correlated with CD activity. Disease activity was measured by the Pediatric CD Activity Index (PCDAI). Given the potential confound of higher dose steroids, sub-analyses excluded subjects on ≥ 20 mg/day prednisone-equivalent (n=34).

Results—Total CDRS-R scores in the overall sample significantly decreased over time after both treatments (p<0.0001). Treatment with CBT was associated with a significantly greater

Corresponding Author: Eva Szigethy, M.D., Ph.D., Children's Hospital of Pittsburgh, 4401 Penn Avenue, 3rd Floor Plaza Building, Pittsburgh, PA 15224; Phone 412 692-8147; Fax 412 692-6913; szigethye@upmc.edu.

Conflicts of Interest

Drs. Bujoreanu, Youk, Keljo, Srinath, Bosuvaros, DeMaso, Fairclough Jones, Lotrich and Mr. Ducharme report no relevant conflict of interests.

improvement in the PCDAI ($p=0.05$) and somatic depressive subtype ($p=.03$) in those with active IBD ($n=95$) compared to SNDT. After excluding those on steroids ($n= 34$), there was a significant improvement in total CDRS-R ($p=0.03$) and in PCDAI ($p=0.03$) after CBT.

Conclusions—Psychotherapy may be a useful adjunct to treating depression in the context of CD-related inflammation in youth who are not concurrently on higher dose steroids.

Keywords

depression; inflammation; physical illness; psychotherapy; inflammatory bowel disease; Crohn's disease; somatic depressive symptoms

INTRODUCTION

Given that physical illnesses with co-occurring clinical depression are associated with significantly poorer medical outcomes and reduced quality of life in children and adolescents,¹⁻³ there is a critical public health need to explore the effectiveness of evidence-based psychiatric interventions on their healthcare. One such physical illness is inflammatory bowel disease (IBD), which is a life-long troubling pediatric physical illness characterized by episodic inflammation of the gastrointestinal tract with bloody diarrhea, abdominal pain, fever, and fatigue.⁴ Treatment of IBD often requires anti-inflammatory agents such as systemic corticosteroids⁵ and surgery for severe disease activity. Youth with IBD have higher rates of clinical depression compared to healthy children or to children with other chronic physical illnesses.⁶⁻⁸

The effects of systemic inflammation on the brain have been conceptualized as one explanation for the relatively higher rates of depression in IBD.⁹ A mechanistic relationship between disease activity and depression has growing support, particularly for clusters of somatic depressive symptoms (e.g., fatigue, sleep disturbance, anhedonia), both in the absence^{10,11} and presence^{12,13} of physical diseases, including IBD.^{7,14-16} In fact, these somatic symptoms may be a marker of more severe disease activity. During periods of extreme disease activity, there may be phylogenetic reasons for organisms to “shut down” in order to conserve energy, to shift motivated behavior towards recuperation and care seeking to promote the organism's optimal healing¹⁷.

Though Crohn's disease (CD) and ulcerative colitis (UC) are characterized as IBD subtypes and share many clinical features, each has different underlying inflammatory pathophysiologies.^{18,19} For example, lesions in CD can involve all layers of the gastrointestinal mucosa and are associated with more systemic inflammation, while UC lesions are more superficial with disease activity less frequently reflected by elevated inflammatory markers. Such phenotypic heterogeneity makes it more challenging to evaluate if cognitive behavioral therapy (CBT) has any selective benefits over supportive non-directive therapy (SNDT). In a recent randomized trial comparing CBT to SNDT for clinically depressed youth with either CD or UC, we found significant improvements for both interventions in depression severity, global functioning, quality of life, and disease activity.²⁰ However, the only statistically significant difference between treatments was a

greater reduction in the pooled disease activity in the CBT group, in a setting of mild disease activity at baseline.

In states of milder inflammation, depressive symptoms, even somatic ones, have been shown to improve after CBT in youth with IBD in an open trial^{21,22}. These findings are consistent with the concept that teaching coping skills by targeting behavioral activation and cognitive reframing, the two predominant components of CBT, may be a viable pathway in improving underlying depression under these conditions.

The current study is a secondary analysis of a subsample of adolescents with CD, representing 74% of the original sample²⁰ with more systemic inflammation due to transmural gut wall involvement. The current study extends our previous work by evaluating if there were differences in improvement in overall depression, somatic depressive symptoms associated with CD activity, and systemic inflammation between CBT and SNTD interventions. We postulated that both interventions would reduce depression, but that CBT would have a greater impact on reducing depression overall in the sample, conceptualizing that taught coping skills, such as behavioral activation and cognitive reframing, would help make participants more active agents in controlling modifiable factors in their physical illness experience. We hypothesized further that somatic depressive symptoms would show the greatest degree of improvement after CBT in the presence of disease activity. That is, when learning to cope, a participant would be able to counter the brain manifestations of CD more than through non-directive sharing about their illness (SNTD). Because systemic steroids, particularly at higher doses, can also have a confounding effect on treatment outcomes as they have been shown to have an independent negative effect on emotional and cognitive functioning in daily life in treating youth with IBD,²³ we analyzed the data also excluding those on the higher dose steroids at baseline. We postulated that CBT would be associated with an even greater change in depressive severity in this sample.

MATERIALS AND METHODS

Participants

Youth ages 9-17 years with either CD or UC and their parents were recruited from Children's Hospital of Pittsburgh and Boston Children's Hospital between 2008 and 2012 using a protocol approved by the Institutional Review Boards at both sites. The eligibility criteria, trial methods, and outcomes have been previously described.²⁰ Participants were screened for depression with the Children's Depression Inventory (CDI);²⁴ those with CDI scores ≥ 10 were interviewed within two weeks using the Kiddie-Schedule for Affective Disorders and Schizophrenia for Children, Present Version (KSADS-PL).²⁵ Youth were included in the trial if they met criteria for major or minor depression by DSM-IV-TR criteria.²⁶

Design

This study represents a secondary analysis of the data collected as part of the randomized trial comparing CBT and SNTD for the treatment of depression and quality of life, functioning, and disease activity in a sample of youth with IBD. In the parent study, eligible

subjects with CD (n = 161) or UC (n= 56) were randomized to receive a 12-week course of either modified CBT or SNTD and were assessed with an identical battery of measures at baseline and at intervention completion (3 months). This study focuses on the CD cohort using depression and disease activity as outcomes for hypothesis-generating analyses.

Measures

Depression—The **Children's Depression Inventory** (child and parent-report version) is a 27-item self-report questionnaire assessing the presence and severity of depressive symptoms.²⁴ CDI scores ≥ 10 on either child or parent rating were considered as reflective of clinically significant depressive symptoms.

The Kiddie-Schedule for Affective Disorders and Schizophrenia-Present Version is a semi-structured diagnostic interview for youth and parents assessing for the presence of psychiatric disorders based on DSM-IV criteria.²⁵ Depression remission was defined as no longer meeting KSADS-PL criteria for depressive diagnosis post-treatment.

The **Children's Depression Rating Scale-Revised** (CDRS-R), a semi-structured clinician-rated instrument assessing depressive severity,²⁷ was chosen as the primary emotional outcome because it has been shown to differentiate depressive from physical symptoms.²⁸ CDRS-R scores can range between 17-113 with values < 28 are consistent with remitted depression.

Disease Activity—CD onset, presentation and course, gastrointestinal tract disease location, medication use (*e.g.*, corticosteroids, biological therapies, and/or immunomodulators), surgical history, and ostomy status were obtained from parents and medical record verification. Subjects with ≥ 20 mg of prednisone or systemic steroid equivalent at baseline were defined as having higher-dose steroid utilization. Biomarkers of systemic inflammation erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded from the medical record by a blinded gastroenterologist. Pertinent demographic information were recorded from parent reports and verified in the medical record.

The **Pediatric Crohn's Disease Activity Index (PCDAI)** is a well-validated scale used to determine disease activity in CD and has been shown to correlate significantly with gastrointestinal inflammation.^{29,30} It measures three domains during medical visits: 1) self-report of pain and stool consistency, 2) functional disability, and 3) objective physical/biochemical data (such ESR, hematocrit, albumin, growth, and physical examination). Rated by a blinded gastroenterologist PCDAI scores ≥ 30 were considered to indicate moderate disease activity, scores in the range of 11-29 reflected mild disease activity, and scores < 10 were indicative of inactive disease.³¹ Disease activity (PCDAI), ESR, and CRP were extracted from the medical record of a gastroenterology visit only if this visit was within 1 week of the baseline assessment and within 2 weeks of the post-treatment (3-month) assessment.

Interventions

Randomized subjects underwent up to 12 weekly of either CBT sessions^{22,32} or SNDT. Therapists (n=10) experienced in treating physically ill youth were trained in both manual-based interventions and received weekly supervision. All sessions were audiotaped to allow for quality assurance and to assure treatment fidelity. Each treatment was tailored to the developmental level of each youth. Up to 75% of sessions could be completed by telephone. More detailed descriptions of each intervention have been described previously.⁵²

Statistical Analyses

Descriptive statistics were computed for all demographic and clinical measures. T-tests were used for continuous variables and chi-square tests (or Fisher's Exact tests) for categorical variables to assess baseline differences between the two treatment groups. To assess how somatic depressive symptoms responded to psychotherapy, we created a somatic subscale of the CDRS-S by combining the somatic items of the CDRS-R that were statistically significantly correlated with baseline CD activity. The criteria for inclusion were defined as the CDRS-R items which correlated with total PCDAI score with a coefficient of >0.2 ($p < 0.01$).

Linear mixed effects models were used to assess the impact of treatment (CBT versus SNDT) on CDRS-R over time (baseline to 3 months) in intent-to-treat analyses. Change from baseline CDRS-R scores was modeled as a function of time and the interaction of treatment and time. Because subjects were randomized into each treatment group (there were no baseline group differences), baseline outcome scores for each treatment were set to be equal in the models by not including the main effect of treatment. Effect sizes for the treatment impact on outcomes of interest were computed using Cohen's d estimates. Similar models were also fit to assess the impact of treatment on disease activity (using PCDAI scores as the outcome) and on the somatic depressive subscale. Exploratory linear mixed models were fit to evaluate separately the change in the depressive outcomes (total CDRS-R and somatic CDRS-R subscale) over time within two groups of disease activity: inactive (PCDAI ≤ 15) versus active (PCDAI >15). Models were also fit within the subgroup of youth who were not on higher dose systemic steroids at baseline.

All models were adjusted for site. Statistical significance was determined using Wald tests (z-tests) from the linear mixed models using $\alpha=0.05$ (two-sided). No correction was made to account for multiple comparisons because all analyses in this study were for hypothesis-generation purposes. All analyses were performed using Stata version 12.³³

The sample size determination for the main study was based on two-tailed tests of hypotheses with size $\alpha = 0.05$ (Cohen, 1988; Kraemer, 1997) using a repeated measures design with estimated correlation between the time points of 0.6. The expected effect for CBT for our primary outcome (CDRS-R) was estimated to be large (Cohen's $D > 0.8$). The expected effect for SNDT for our primary outcome was estimated to have small to moderate effect size (range of Cohen's $D=0.2-0.4$). The effect size for CBT versus SNDT was then estimated as the difference between these separate effects, thus giving moderate effect sizes

of Cohen's $D=0.4$ to 0.6 . Based on our current sample size for CD of $n=161$, using the original estimated effect sizes the power ranged from 81-99%.

RESULTS

Sample characteristics

In the parent study, a total of 765 unique subjects with IBD were screened (550 with CD) with a total of 217 meeting criteria for randomization. From the 161 with CD, 82 were randomized to CBT and 79 to SNT. At 3 months, 69 youth completed CBT and 66 completed SNT treatments. PCDAI information was unavailable for 5 participants at baseline and for 26 participants at month 3.

Participant characteristics at baseline are shown in Table 1. Mean age was 14.3 years ($SD=2.4$), race was predominantly white (87.6%) and there was moderate depressive severity ($CDRS-R=46$, $SD=12.1$). Active systemic inflammation was evident by the mildly elevated ESR and CRP. The mean sample PCDAI score of 21.7 ($SD=16.5$) was consistent with mild disease activity. In the subgroups consisting of no ($n=119$) or low-dose (range 5-15mg; $n=8$) systemic corticosteroids, the mean PCDAI score was 18.9 ($SD=14.5$), consistent with mild disease activity. Analyses were completed on total sample and excluding subjects on 20mg/day prednisone-equivalent ($n=34$). The somatic depressive symptom subtype consisted of CDRS-R items 2 (anhedonia), 4 (sleep), 5 (appetite), 6 (fatigue), 7 (physical complaints), 11 (depressed feelings) and 14 (excessive weeping) (Table 2). While suicidal ideation (Item 13), also correlated with total PCDAI ($r=0.17$; $p=.032$), it did not meet the threshold level to be included in the somatic subtype.

Per KSADS-PL, comorbid psychiatric diagnoses included generalized anxiety disorder (20.5%), specific phobias (14.9%), attention deficit hyperactivity disorder (11.6%), separation anxiety disorder (9.7%), oppositional defiant disorder (8.9%), social anxiety disorder (8.8%), obsessive compulsive disorder (1.9%), dysthymia (1.4%), post-traumatic stress disorder (1.4%), anorexia nervosa (0.9%), panic disorder (0.5%) and conduct disorder (0.5%) (data not shown).

Approximately 75% of all psychotherapy sessions were delivered by phone instead of face-to-face (data not shown). The most common reason reported by subjects for choosing phone sessions in both therapy arms was the convenience of not having to travel to the hospital. To evaluate if this choice was due to more severe disease activity, we evaluated the percentage of phone sessions by PCDAI level (inactive versus active) using a linear regression model at baseline with percent phone sessions as the outcome and PCDAI activity level as the independent categorical variable. CD activity was not significantly associated with the percentage of phone sessions ($p=0.052$) (data not shown).

Intervention effects on depressive severity and disease activity

There were statistically significant differences by site for disease activity (PCDAI) at baseline ($p<0.0001$) and at month 3 ($p=0.002$) with the Pittsburgh site having more severe disease. There were no statistically significant differences between sites for steroid use (data not shown).

For the total CD sample, both treatments showed similar improvement in depressive severity (CDRS-R), with no significant difference between the interventions ($z=1.78$, $p=0.07$; Table 3). CDRS-R significantly improved over time for both CBT ($\beta=-15.26$; $z=-9.28$; $p<0.0001$) and SNDT ($\beta=-14.46$; $z=-7.71$; $p<0.0001$) (data not shown).

Within categories of baseline disease severity (inactive versus active), no statistically significant differences in CDRS-R between the treatments were found for the whole sample ($p=0.07$ for active disease, favoring CBT and $p=0.40$ for inactive disease). Both CBT and SNDT resulted in reductions in CDRS-R for both disease activity groups.

To evaluate if there were differences to psychotherapy response to symptoms more related to disease activity (somatic depressive symptoms) over time, factor-specific linear mixed models were fit using the somatic depressive symptom subtype as the outcome in the total sample and within each PCDAI activity (inactive versus active). There was no specific treatment effect for the somatic depressive symptoms in the total sample or those with inactive CD; however somatic symptoms showed a significantly greater improvement with CBT in the subgroup with active CD ($p=0.03$).

For the total CD sample, there was a significant change in PCDAI over time for CBT ($\beta=-11.64$; $z=-5.35$; $p<0.0001$) and for SNDT ($\beta=-7.31$; $z=-3.12$; $p=0.002$) (data not shown). CBT had a selective significant impact on improving PCDAI ($z=1.97$, $p=0.05$; Table 3) as well as ESR ($p=.004$; $n=103$; data not shown). CBT was also favored but not statistically significant for decreasing CRP ($p=0.07$; $n=97$; data not shown). The total baseline PCDAI score was significantly correlated with both CRP ($r=.32$, $p=0.0002$; $n=135$) and ESR ($r=.50$; $p<0.00001$; $n=148$).

When youth on systemic steroids (≥ 20 mg per day) at baseline ($n=34$) were excluded, both interventions again significantly improved depressive severity and disease activity (Table 3) for the whole subsample. However, CBT had a significant greater impact than SNDT on reducing total CDRS-R ($z=2.18$, $p=0.03$) and somatic depressive symptoms ($z=2.14$, $p=0.03$), and on improving PCDAI ($z=2.15$, $p=0.03$).

DISCUSSION

Our findings show that in youth with CD, both CBT and SNDT were associated with a reduction of depression and disease activity over three months of psychiatric treatment with only CD activity and systemic inflammation (ESR) demonstrating a statistically significant improvement after CBT compared to SNDT. These results are similar to what we found in the original study sample, which included youth with UC²⁰, and suggest that the modality of psychotherapy used for depression in chronic pediatric physical illness is not important. Even when youth with CD were divided into more homogeneous subgroups (those with and without active CD at baseline), there was no statistically significant difference in the change in depressive severity between the two psychotherapies. Given the association that has been found between depressive severity and IBD activity^{7,34}, it was surprising that depressive severity did not parallel changes in CD activity by not showing a statistically significant greater improvement after CBT.

Depression is a heterogeneous entity with different depressive symptom clusters associated with different clinical factors. Our previous work using person-centered analyses to characterize different depressive subtypes in a predominantly CD cohort found that youth with a depressive subtype consisting of somatic depressive symptoms had higher levels of inflammation than those with other types of depressive profiles.³⁵ Somatic depressive symptoms have been reported to be associated with inflammation both in animal models of colitis and humans with other conditions linked to inflammatory processes such as patients with hepatitis treated with pro-inflammatory protein (interferon, an exogenous cytokine).^{36,37}

We evaluated the somatic depressive symptoms which significantly correlated with CD activity to assess whether there were differential psychotherapy effects favoring CBT. Our analyses showed that mood symptoms and somatic symptoms (e.g., anhedonia, fatigue, sleep disturbance, and appetite changes) were most significantly correlated with active CD and likely represent the effects of immune activation in the brain. In examining changes in these somatic symptoms to psychotherapy, while there was no statistically significant difference between treatments in the total CD sample, there was a statistically significant difference favoring CBT in the 95 youth with active CD (Figure 1). These findings suggest that in the context of active IBD, depressed adolescents with a preponderance of somatic depressive symptoms have a greater benefit from CBT while those in remission or with other types of depressive symptoms benefit more generally from psychosocial interventions that are not modality specific. A review of brain-gut interactions in IBD suggests that psychosocial interventions may have a role in treating neuropsychiatric symptoms associated with inflammation by altering stress response and by the anti-inflammatory effects of vagal activation.⁹

The differential improvement of depression after CBT versus SNT in the context of disease activity is clinically relevant. We conceptualize that a more didactic therapeutic approach which targets behavioral activation, active problem-solving, relaxation, and cognitive reframing as ways of improving perceived control may be more useful than the more empathic active listening ingredients of the supportive therapy. While psychotherapy studies of depressed adolescents without physical illness identified some of these skills e.g., exercise, problem-solving, improving sense of self-efficacy as “active ingredients”³⁸, future component analysis of the psychotherapy content and process will be needed to evaluate which specific CBT skills most benefited which subset of depressed adolescents with IBD.

In the current study, the selective association of somatic symptom severity with baseline inflammatory activity, and the statistically significant improvement in inflammation (ESR) after CBT treatment support the notion that the improvement in disease activity was related to inflammation-related IBD symptoms. These results replicate our previous findings of CBT effects on IBD activity in youth with subsyndromal depression²² and are also consistent with findings in a depressed adult cohort where depression improved significantly more with anti-inflammatory drug treatment compared to placebo only in the setting of elevated CRP.³⁹ Thus, it is conceivable that depressed youth with mild to moderate IBD activity are similar to depressed patients who have mild elevation in circulating inflammatory biomarkers but no systemic disease. Future studies are needed to investigate

psychotherapy effects under these conditions as well as effects on specific depressive symptoms such as anhedonia or fatigue.

One proposed pathway of action for the differential effect of CBT in the context of systemic inflammation is via increasing the parasympathetic tone. Vagal stimulation, in patients with rheumatoid arthritis and in animal models of colitis, has been shown to have potent anti-inflammatory effects^{9,40-43} and there is a growing literature supporting anti-inflammatory effects of other types of psychosocial interventions,⁴⁴⁻⁴⁶ though the underlying pathways remain to be elucidated. Future studies evaluating treatment mediators will need to target such mechanisms^{9,44} by replicating these findings in larger samples recruited and randomized based on depressive subtypes or profiles.

Systemic steroids at higher doses can have confounding direct negative effects on the brain.²³ When the 34 youth on higher dose steroids were systematically excluded from analyses, there was a significantly greater improvement in overall depressive severity in the total sample as well as in those with active IBD after CBT. Systemic steroids are often used to treat severe IBD flares and thus this steroid subgroup could represent the subgroup where depression is serving a protective effect to facilitate healing and thus is not as amendable to psychosocial interventions.

Although no randomized trials of antidepressant treatment have been conducted with patients with IBD, animal models of colitis using several different classes of antidepressants (e.g., serotonin reuptake inhibitors, bupropion) have shown that these antidepressants have anti-inflammatory properties in the gastrointestinal tract⁴⁷⁻⁴⁹. Studies of serotonergic antidepressants in other models of inflammatory depression, however, have not shown positive effects on somatic symptoms.¹⁶ In adults with CD, an open trial of bupropion targeting dopaminergic circuits showed favorable effects on both depression and CD activity.^{50,51} Interestingly, dopaminergic pathways connecting basal ganglia with cortical regions have been implicated in other models of inflammatory depression⁵²⁻⁵⁴ and may be one possible pathway by which CBT exerts an effect. Again, future studies will need to evaluate the role of psychotropic agents as an adjunct to psychotherapy in decreasing inflammation and depression in this population (e.g., fatigue, sleep disturbance, pain).

A potential limitation of the study is that CD activity was recorded from the medical charts and not as part of the research protocol, so there are subjects with missing data. However, the CD activity data which was available from the clinical record at the time of the depressive screen was reviewed by a gastroenterologist blinded to study therapy assignment. Another possible limitation is the lack of adjustment for the overall level of statistical significance of the study for multiple comparisons as the study was hypothesis generating in nature.⁵⁵ However, the importance of our findings goes beyond statistical significance given its clinical relevance for the development of concept-driven interventions focused on understanding the treatment of depression in inflammatory conditions. The finding of increased CBT efficacy under conditions of mild inflammation can have applicability for patients with endogenous depression who may have mildly elevated systemic inflammation.³⁹ While it is possible that improvement of depression over time in both psychotherapeutic treatments represents regression to the mean independent of the effects of

either intervention, the favoring of CBT in these subgroups of patients argues against an absence of impact. Adding placebo-controlled or treatment as usual arms in randomized treatment trials would help to resolve this question. Finally, larger samples would also allow for more rigorous testing of treatment response confounders such as steroids, biologics, and other immunomodulatory agents used to treat CD.

CONCLUSION

Depression in physical illnesses, like IBD, is a significant public health problem that is common, disrupts normal development, and causes substantial functional impairment. This study provides evidence that psychotherapy, regardless of the specific modality, can be a useful adjunct to the healthcare of youth with IBD both in addressing associated depression and illness severity. More specifically, CBT may be best fitted to treat overall depression and somatic depressive symptoms in youth with inflammation, while empathic support and/or CBT can help during periods of inactive or more severe inflammation.

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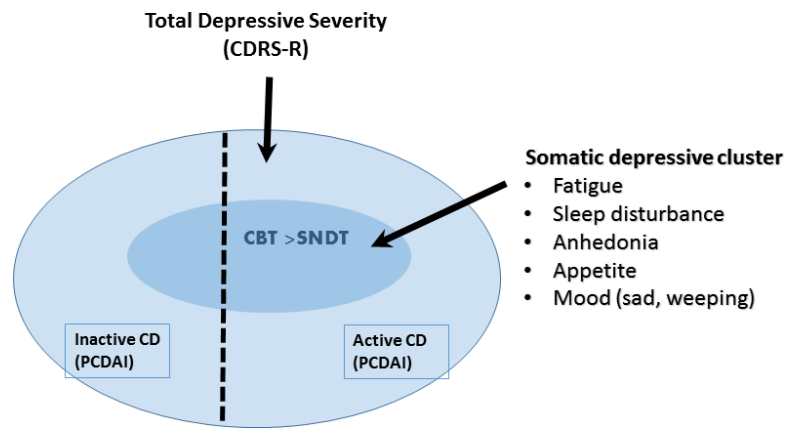


Figure 1. Cognitive behavioral therapy (CBT) associated with more significant improvement in somatic depressive symptoms in the presence of active Crohn's disease (CD) compared to supportive non-directive therapy (SNDT).

Table 1

Baseline Demographic, Clinical and Psychosocial Characteristics of Patients with Crohn's disease by Treatment Group (n=161)

| Measure | Total Sample (n=161) | | CBT (n=82) | | SNDT (n=79) | | Statistic, p-value |
|-------------------------------------|----------------------|---------------|------------|---------------|-------------|---------------|------------------------|
| | N (%) | Mean (SD) | N (%) | Mean (SD) | N (%) | Mean (SD) | |
| Demographics | | | | | | | |
| Age | 161 | 14.3 (2.4) | 82 | 14.1 (2.6) | 79 | 14.4 (2.3) | t=-0.85, 0.39 |
| Gender (Male) | 75 (46.6) | -- | 41 (50.0) | -- | 34 (43.0) | -- | $\chi^2(1)=0.78, .38$ |
| Site (Pittsburgh) | 104 (64.6) | -- | 53 (64.6) | -- | 51 (64.6) | -- | $\chi^2(1)=.001, 0.99$ |
| Race (White) | 141 (87.6) | -- | 77 (93.9) | -- | 64 (81.0) | -- | $\chi^2(1)=6.14, 0.01$ |
| Depression | | | | | | | |
| CDI Child (Self Report Depression) | 160 | 13.59 (6.72) | 81 | 13.05 (6.64) | 79 | 14.15 (6.80) | t=-1.04, 0.30 |
| CDI Parent (Self Report Depression) | 160 | 14.61 (6.45) | 82 | 14.61 (6.26) | 78 | 14.60 (6.69) | t=0.01, 0.99 |
| CDRS-R | 161 | 46.01 (12.05) | 82 | 44.31 (11.64) | 79 | 47.76 (12.28) | t=-1.82, .07 |
| Major Depression | 103 (64.0) | -- | 52 (63.4) | -- | 51 (64.6) | -- | $\chi^2(1)=0.02, 0.88$ |
| Minor Depression | 58 (36.0) | -- | 30 (36.6) | -- | 28 (35.4) | -- | |
| Disease Activity | | | | | | | |
| CD Activity (PCDAI) | 153 | 21.70 (16.51) | 79 | 21.01 (16.17) | 74 | 22.43 (16.94) | t=-0.53, 0.60 |
| Erythrocyte sedimentation rate | 148 | 23.10 (17.24) | 74 | 23.14 (16.17) | 74 | 23.07 (17.86) | t=0.02, 0.98 |
| C-reactive protein | 135 | 1.54 (2.68) | 68 | 1.55 (3.08) | 67 | 1.53 (2.23) | t=0.04, .97 |
| Crohn's Disease Medications | | | | | | | |
| Systemic Corticosteroids | 34 (21.1) | -- | 17 (20.7) | -- | 17 (21.5) | -- | $\chi^2(1)=0.02, 0.90$ |
| Biological Therapies | 47 (29.2) | -- | 22 (26.8) | -- | 25 (31.7) | -- | |
| Immunomodulators | 84 (52.2) | -- | 42 (51.2) | -- | 42 (53.2) | -- | $\chi^2(1)=0.06, 0.81$ |
| Surgery (yes) | 17 (10.7) | -- | 4 (4.9) | -- | 13 (16.7) | -- | FE p=0.02 |
| Ostomy (yes) | 4 (2.5) | -- | 0 (0.0) | -- | 4 (5.1) | -- | FE p=0.06 |

CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; PCDAI = Pediatric Crohn's Disease Activity Index; FE= Fisher's Exact

Table 2

Correlation between individual depressive symptoms on CDRS and PCDAI at baseline.

| CDRS-R Item | Description | r | p |
|-------------|---------------------|-------------|-------------|
| 2 | Anhedonia | 0.22 | .007 |
| 4 | Appetite | 0.23 | .005 |
| 5 | Sleep | 0.34 | .001 |
| 6 | Fatigue | 0.23 | .005 |
| 7 | Physical complaints | 0.35 | .001 |
| 11 | Depressed mood | 0.26 | .002 |
| 14 | Weeping | 0.33 | .001 |
| 1 | Schoolwork | 0.05 | .546 |
| 3 | Social withdrawal | 0.01 | .915 |
| 8 | Irritability | 0.03 | .701 |
| 9 | Guilt | -0.04 | .603 |
| 10 | Self esteem | -0.06 | .475 |
| 12 | Morbid ideation | 0.03 | .680 |
| 13 | Suicidality | 0.17 | .032 |

Pearson correlation coefficients (r) and respective p-values are presented with bolded values representing the somatic/mood symptoms showing significant association at p<0.01 level.

Table 3

Effect of treatment (CBT versus SNTD) over time controlling for site.

| Outcome | N | Treatment effect coefficient (β) | 95% CI | Z statistic | p-value for treatment effect over time [*] | Pre-Post Effect Size |
|---|-----|--|-------------|-------------|---|----------------------|
| Total Sample | | | | | | |
| CDRS-R | 161 | 3.54 | -0.35, 7.44 | 1.78 | 0.07 | 0.13 |
| CDRS-R Somatic | 161 | 2.22 | -0.23-4.67 | 1.77 | 0.08 | 0.22 |
| CD Activity | 156 | 5.27 | 0.03, 10.52 | 1.97 | 0.05 | 0.29 |
| Subgroup of subject without higher dose steroids at baseline | | | | | | |
| CDRS-R | 127 | 4.77 | 0.48, 9.07 | 2.18 | 0.03 | 0.20 |
| CDRS-R Somatic | 127 | 2.87 | 0.24-5.50 | 2.14 | 0.03 | 0.34 |
| CD Activity | 122 | 5.54 | 0.49, 10.60 | 2.15 | 0.03 | 0.28 |
| Subgroup of total subjects with active CD at baseline | | | | | | |
| CDRS-R | 95 | 4.83 | -0.31-9.98 | 1.84 | 0.07 | 0.23 |
| CDRS-R Somatic | 95 | 3.52 | 0.34-6.70 | 2.17 | 0.03 | 0.42 |
| Subgroup of total subjects with inactive CD at baseline | | | | | | |
| CDRS-R | 58 | 2.76 | -3.70-9.21 | 0.84 | 0.40 | 0.02 |
| CDRS-R Somatic | 58 | 0.98 | -3.00-4.97 | 0.48 | 0.63 | 0.06 |

CBT= cognitive behavioral therapy; SNTD= supportive non-directive therapy

* CBT was favored over SNTD in all of these outcomes.