Efficacy of Attachment-Based Family Therapy compared to Treatment as Usual for
Depressed Adolescents in Community Mental Health Clinics

Luxsiya Waraan¹, Erling W. Rognli^{2,3}, Nikolai Olavi Czajkowski^{4,5}, Marianne Aalberg¹ and
Lars Mehlum⁶

¹Division of Mental Health Services, Akershus University Hospital, Lørenskog, Norway

²Department of Psychology, University of Oslo, Oslo, Norway

³Department of Child and Adolescent Mental Health Services, Akershus University Hospital,
Lørenskog, Norway

⁴PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo,
Norway

⁵Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway

⁶National Centre for Suicide Research and Prevention, Institute of Clinical Medicine,
University of Oslo, Oslo, Norway

Corresponding Author:

Luxsiya Waraan

PhD candidate, Cand.psychol

Division of Mental Health Services,

Akershus University Hospital,

P.O. 1000, 1478 Lørenskog, Norway

E-mail: lusi@ahus.no

Phone: + 47 45451585

Abstract

Background: Major Depressive Disorder (MDD) is a disabling mood disorder, profoundly affecting a large number of adolescent's quality of life. To date, no obvious treatment of choice for MDD in adolescents is available and progress in the treatment of depressed adolescents will have important public health implications. Attachment-Based Family Therapy (ABFT), as the only empirically supported family therapy model designed to treat adolescent depression, aims to repair interpersonal ruptures and rebuild an emotionally protective parent-child relationship.

Objective: To study the efficacy of ABFT compared with Treatment as Usual (TAU) delivered within child- and adolescent mental health services (CAMHS) to adolescents with MDD.

Method: Sixty adolescents, aged 13-18 years, with MDD referred to two CAMHS were randomized to receive 16 weeks of ABFT or TAU. ABFT consisted of weekly therapy sessions (family/individual or both) according to the treatment manual. TAU was not monitored. Primary outcomes were clinician-rated (Hamilton Depression Scale, HAMD) and self-reported (Beck Depression Inventory-II, BDI-II) depressive symptoms assessed at baseline and post-treatment by blinded evaluators for HAMD and at baseline, and after 4, 6, 8, 10, 12, 14, and 16 weeks for BDI-II. Analyses were performed according to intent-to-treat principles.

Results: At post-treatment, clinician-rated remission rates on the HAMD (5 % in ABFT and 3.33% in TAU, $p=1$, OR=1.54, Fisher's exact test) and self-reported symptoms of depression on the BDI-II did not differ significantly between groups ($X^2[2, N = 60] = 0.06$, $p = 0.97$). In both treatment groups participants reported significantly reduced depressive symptoms, but the majority of adolescents were still in the clinical range after 16 weeks of treatment.

Treatment of Depression in Adolescents

Conclusion: In this sample of adolescents treated for MDD in community mental health clinics, ABFT was not associated with more favorable outcomes than TAU in terms of remission rates on clinician rated and self-reported depressive symptoms. Remission and response rates were low in both groups, suggesting a need for continued improvement of the treatment methods.

Trial Registration:

Clinicaltrials.gov identifier: NCT01830088

<https://clinicaltrials.gov/ct2/show/NCT01830088?term=Villab%C3%B8&draw=2&rank=1>

Date of registration: April 12, 2013

Keywords: Depression, Adolescents, Attachment Based Family Therapy, Efficacy trial

Treatment of Depression in Adolescents

Depressive disorders entail persistent emotional, biological, and psychological symptoms, accompanied by impaired social functioning (1) and are among the most common psychiatric disorders in adolescents. Nearly 6 % of all adolescents meet criteria for Major Depressive Disorder (MDD) at any given time (2). The prevalence of MDD increases with the onset of puberty and affects nearly twice as many girls as boys (3). Experiencing MDD during adolescence increases the risk of further episodes of depression as an adult (4). MDD is associated with significant disability, morbidity and mortality globally(5), and has been identified as a major risk factor for suicidal behavior and death by suicide (6). Given the high prevalence and substantial burden of depression in adolescents, developing effective interventions that are feasible to implement in community mental health settings is a high priority.

Variations of cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have been most widely researched and identified as empirically supported psychotherapy approaches to treat adolescents with depression (7). With the accumulation of empirical data from randomized controlled trials (RCT) over the past decades, several meta-analyses on treatment of adolescents with depression suggest CBT and IPT to be efficacious treatments with moderate effect sizes (8-14). CBT and IPT are efficacious for adolescents with MDD when adequately implemented, but response rates are moderate (around 60 % in clinical trials) and a substantial proportion of adolescents fail to remit (15). Even when treatment is successful, relapse rates are high (16-18), underscoring the need for continued efforts to develop and improve treatments.

One consideration in the effort to improve treatment for MDD in adolescents is a greater focus on parental involvement in therapy. Parents can play an important role in the development and maintenance of depressive symptoms in adolescents (19, 20). Family-based interventions, therefore, have a significant potential to address known risk factors for

Treatment of Depression in Adolescents

adolescent depression and could be an effective way of engaging adolescents in treatment.

Attachment-based family therapy (ABFT), developed by Diamond et al. (2002), is a treatment that focuses on helping families identify and resolve core family conflicts and attachment ruptures that have inhibited adolescents from trusting their parents and using them as a source of emotional support. ABFT is primarily a process oriented, emotion focused treatment, guided by a semi-structured treatment protocol. The model aims to both improve adolescents' and parents' functioning and interactional processes which are important to create a favourable context for individual development.

The empirical support for ABFT is growing (21-24) and ABFT has been designated as a probably efficacious treatment for adolescents with suicidal ideation based on a study from 2010 (Diamond et al., 2010; Glenn, Franklin, & Nock, 2015). Nevertheless, the evidence is still limited and inconclusive. In the first randomized clinical trial of ABFT where 12 weeks of ABFT was compared to a 6-week waitlist in a sample of 32 adolescents with MDD (22), participants who received ABFT reported significantly lower levels of depressive symptoms and had to a larger extent remitted from depression at post- treatment compared to participants in the waitlist group. Several weaknesses of this study, such as the small sample size, using waitlist as comparison condition and the duration of the waitlist being only half of the duration of the active treatment, precluded firm conclusions about efficacy of the treatment. In a second study (23), 66 adolescents were randomized to ABFT or enhanced usual care. Although participants who received ABFT exhibited greater and faster reduction in suicidal ideation, ABFT was no more effective in reducing symptoms of depression compared to enhanced usual care. In a more recent study comparing the efficacy of ABFT to a family-enhanced nondirective supportive therapy (FE-NST), both treatments produced substantial reductions in depressive symptoms, but ABFT did not outperform FE-NST in reducing suicidal ideation, which was the primary outcome in the study (21). So far ABFT

Treatment of Depression in Adolescents

has not been empirically validated when implemented outside the context of the treatment developers or in other countries than the USA. In the current study, we aimed to examine the efficacy of ABFT compared to treatment as usual (TAU), an active control treatment, in reducing depressive symptoms in adolescents with MDD. Our primary hypothesis was that more adolescents treated with ABFT would remit from depression compared to adolescents who received TAU.

Method

The present study was a two-arm, parallel groups randomized trial comparing ABFT with TAU. The study was approved by the regional committee for medical research ethics, South-Eastern Norway. Participating adolescents and their families were recruited among adolescents referred to two child- and adolescent mental health service (CAMHS) clinics in South-Eastern Norway. The clinics were publicly funded, and all treatments were provided free of charge by the universal health insurance system of Norway. Inclusion criteria were 1) a current major depressive episode, 2) a score above 15 on the Grid Hamilton Depression Rating scale (GRID-HAMD, 25) and 3) currently living with their primary caregiver. Exclusion criteria were a diagnosis of any psychotic disorder, eating disorder, bipolar disorder, intellectual disability or pervasive developmental disorder.

Participants

During the pre-specified recruitment period, September 2013 to January 2016, all referrals of adolescents (13 - 18 years) were examined for mentions of depression or core depressive symptoms (depressed mood, anhedonia, or fatigue). Through the use of the Affective Problems subscale on the Youth Self-Report (26) routinely administered by the CAMHS, adolescents with a score >6 were identified in addition to adolescents who were identified as depressed by their referral letters (27). Based on these procedures 276 patients were identified, contacted and checked for study eligibility. Altogether 160 adolescents were

Treatment of Depression in Adolescents

screened with the the Beck Depression Inventory-Second Edition (BDI-II) after which 100 adolescents and their parents went through a full clinical assessment (see CONSORT diagram, Figure 1). They met with a study-affiliated clinical psychologist (either the first or second author) at the CAMHS and written informed parental consent and adolescent assent were obtained. Adolescents and parents were then interviewed separately with a semi-structured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) (28) generating DSM-IV-TR diagnoses. All interviews were video-recorded. Both parents and adolescents completed self-report measures. If the adolescent met inclusion criteria, the assessing clinician conducted randomization by opening a sealed, numbered envelope containing the treatment allocation. Randomization was stratified by clinic, age (13-15 years and 16-18 years), gender, and severity of depression (GRID-HAMD score of ≤ 24 and ≥ 25). Sixty-one participants were finally randomized to either ABFT or TAU in a 1:1 ratio. Shortly after randomization, one patient withdrew consent resulting in a randomized study sample of 60 participants, 30 in each treatment condition.

Parents and adolescents were given feedback on diagnosis and treatment allocation at the end of the assessment session. The assessing clinician answered questions from parents or the adolescent concerning the assessment, and implemented standard safety procedures to the extent deemed necessary. CAMHS staff were then informed of treatment allocation and given a report of the assessment findings, and assigned the case to a study therapist.

Treatments

Treatment consisted of 16 weeks of either ABFT or TAU. ABFT consisted of weekly therapy sessions delivered according to the treatment manual by therapists trained in ABFT for the purpose of the trial. TAU was not manualized and the therapists were free to provide the treatment they considered most appropriate. Both treatments were provided for a

Treatment of Depression in Adolescents

minimum of 16 weeks, but could be extended depending on the therapists' assessment of their patient's needs. For both treatment conditions, results from baseline assessments of psychiatric diagnoses and symptoms were made available to the attending therapist before the first therapy session. If a patient's data indicated high risk of self-harm or suicide, the study staff immediately notified the patient's therapist.

Therapists and therapist training

Over a period of 2 years, 25 (88 % female) therapists delivered the treatments; 19 clinical psychologists, 2 medical doctors, 2 clinical pedagogues, 1 clinical social worker and 1 psychiatric nurse. Therapists delivered either ABFT or TAU only. Therapists varied in their theoretical orientation, including eclectic (40%), cognitive (16%), psychodynamic (4%), or family-oriented (4%) therapy. The therapists had an average of 7.2 years of clinical experience working with adolescents ($SD = 5.73$, range 0 – 18). Eight therapists were trained in ABFT for the purpose of the study. Training consisted of a day-long introductory seminar, followed by a three-day workshop, as well as reading the treatment manual. Therapists were required to have completed one case of ABFT under supervision before treating study patients. All ABFT sessions were videotaped for supervision purposes. Therapists had ongoing supervision by an experienced ABFT therapist, reviewing video recordings of therapy sessions. TAU therapists were recruited from the regular staff of the CAMHS, and treated patients in the trial as part of their regular caseload. TAU was non-monitored and access to supervision varied by clinical experience, but all therapists could discuss cases in multidisciplinary teams.

Assessments

For the duration of the treatment, patients completed self-report measures electronically every other week using a secure online platform (CheckWare Assessment Systems) (29). Some self-report measures were administered occasionally as paper and pencil

Treatment of Depression in Adolescents

questionnaires by the treating clinicians, because of technical difficulties. Post-treatment assessment at 16 weeks was conducted by independent raters (clinical psychologists trained for this purpose) blinded to treatment allocation. Both the main diagnosis and comorbid psychiatric diagnoses were determined based on the K-SADS at baseline, combining information from the adolescent and parent interviews. Interrater reliability was determined by blind scoring of 28 randomly selected videotaped interviews. Interrater reliability for depressive diagnoses based on the K-SADS interview was $\kappa = .56$. The primary outcome measure was severity of depressive symptoms measured by the clinician-rated GRID-HAMD and participants' self-report on the BDI-II. BDI-II was measured every other week through the duration of the trial, while GRID-HAMD was measured at pre- and post-treatment. GRID-HAMD has been shown to have good psychometric properties as a measure of depression severity (25, 30). Intraclass coefficient (ICC) for GRID-HAMD scores was .89 based on a two-way mixed consistency, average measures ICC. GRID-HAMD scores are classified as no depression (0-7); mild depression (8-16); moderate depression (17-23); and severe depression (>24) (31). Clinical response is defined as improvement in GRID-HAMD total score by $\geq 50\%$ from baseline and remission from depression as GRID-HAMD score <5 .

Changes to the protocol

According to the protocol (www.clinicaltrials.gov NCT01830088), we planned to assess the primary and secondary outcomes at weeks 12, 24 and 48. We originally intended to adopt a four week waiting period from randomization to treatment start but this turned out not to be feasible due to the severity of the depressive symptoms for many patients. The treatment period was extended from 12 to 16 weeks, and the first outcome assessment was conducted at week 16 and not 12 as specified in the protocol.

Statistical analysis

GRID-HAMD scores at 16 weeks post randomization were missing for 22 of 60 participants (36.7%). In some cases, adolescents actively declined to provide data. In other cases, when participants did not turn up for scheduled assessment appointments they were not targeted for renewed appointments to collect their data for practical reasons, such as lack of interviewer capacity. We used baseline data to analyse correlates of missingness (32) calculating correlations between a binary coding of missingness for week 16 GRID-HAMD, and the sumscores of a set of baseline variables. We found missingness to be positively correlated with negative self-statements, insomnia and suicidal ideation and negatively correlated with self-reported motivation for talking to a therapist. As we found theoretically plausible predictors of missingness, we adopted the conservative assumption that the data were missing at random (in contrast to missing completely at random, i.e., missingness was conditional on observed random variables), and hence non-ignorable (33). Prior to analyses of the primary outcome variable multiple imputation (34) of the missing data was conducted through chained equations using the package ‘mice’ version 3.3.0 for R version 3.5.1, using the RStudio IDE (35-37). This procedure yields multiple complete datasets with variation in imputed values across the datasets preserving the uncertainty due to data being unobserved. Analyses are repeated across all the imputed datasets and results from these multiple analyses are then pooled for interpretation, allowing estimates of the influence of missing data on the obtained parameter estimates (for a highly accessible treatment of multiple imputation, see 34). Conducting multiple imputation of variables composed of multi-item scales can be challenging. Ideally, imputations should be conducted at the level of individual items (38). However, with several multi-item scales, the number of predictors in the imputation model will often surpass what is feasible with a limited sample size, as the number of predictors approach the number of observations. All variables in the model to be estimated using the multiply imputed data need to be included as predictors in the imputation, and including other

Treatment of Depression in Adolescents

variables as auxiliary predictors is recommended as well (36). Following recommendations of Eekhout and colleagues (39), we set up our imputation with separate imputation of the individual items of the GRID-HAMD only, and passive imputation of the total score, recalculating it iteratively each time the component scores were imputed.

We used baseline GRID-HAMD score, treatment condition and BDI-II and Suicidal Ideation Questionnaire-Junior (SIQ-Jr) (40) scores at 16 weeks as predictors in the imputation model for GRID-HAMD scores on theoretical grounds (33). We examined both individual items and scale scores from other measures, including measures completed by the parents, to select auxiliary predictors for each GRID-HAMD item, as well as for the BDI-II and SIQ-Jr scores at 16 weeks (34). Predictors for imputing any missing values in these predictor variables themselves were selected using the ‘quickpred’ function of the mice package (36). We used the ‘midastouch’ version of predictive mean matching as the imputation method, which has better performance in small sample contexts (41). We imputed 40 datasets, using 50 iterations of the algorithm.

Data were analysed by intent-to-treat (ITT) principles. The primary hypothesis was tested with Fisher’s Exact Test. Linear mixed models were fitted to test whether treatment condition was significantly related to change in scores over time on the primary and secondary outcome variables. For primary outcome measured by GRID-HAMD, which had only two timepoints for the observations, we fitted the model to all the imputed datasets and then pooled the resulting estimates (33). Pooled estimates according to Rubins rules are reported (33). BDI-II had 55% missing across eight timepoints, primary outcomes with multiple observations were analyzed in a mixed modeling framework, handling missing observations using maximum likelihood estimation (32). Variable selection for multilevel analyses was implemented to minimize the information criteria (IC). Since a group mean can conceal changes at an individual level, a Brinley plot (42) was used to visualize within-

subjects effects, from pre- to post-treatment score (Figure 2). The Brinley plot is based on the multiply imputed data set, and the uncertainty of the imputed scores is visualized in the plot.

Analyses were conducted using R (version 3.5.1) and the package lme4 (version 1.1-17) (35, 43) and an alpha level of 0.05.

Results

Table 1 summarizes the baseline sociodemographic data and clinical characteristics of the participants by treatment condition. Mean age was 14.9 (SD = 1.35) and 52 (86.7 %) of the participants were female. For the sixty adolescents who were included, 43 fathers and 57 mothers participated, all adolescents had at least one parent participating in the study. Upon study entry 50 % had one or more comorbid psychiatric diagnosis in addition to the MDD. In both treatment groups all patients completed the 16 weeks of treatment. However, three participants (5 %) in the ABFT and four (7 %) in the TAU condition withdrew from the study, that is, they declined to provide outcome data at the end of treatment.

Primary outcomes

There was no significant difference in the remission rate between ABFT and TAU participants over the 16-week treatment period. Only five (8.33 %) adolescents remitted; 3 (5 %) in ABFT and 2 (3 %) in TAU ($p=1$, OR=1.54, Fisher's exact test). To examine the association between clinician-rated depressive symptoms at posttreatment and treatment condition, a series of linear mixed model analyses with maximum likelihood test were performed (Table 2). Time was entered as fixed effect in model 1, along with a random effect for each adolescent. Time had a significant effect on depressive symptoms $t(90.29) = -3.87$, $p < 0.001$. Model 1 fitted significantly better than a null model ($p < 0.001$). In Model 2, time and treatment condition were entered as fixed effects, along with an interaction effect of time and treatment condition. Model 2 did not fit significantly better than model 1 ($p < 0.98$).

Treatment of Depression in Adolescents

Mean depression scores were reduced from 21.8 (SE = 1.14) at baseline to 17.36 (SE = 1.6) at week 16, but only the coefficient for time ($p < 0.01$) had a significant impact on depressive symptoms. The interaction term of time and treatment group was not significant, $t(92.115) = 0.17$, $p = 0.86$. There was no significant fixed effect of treatment group (ABFT/TAU), $t(112.04) = 0.042$, $p = 0.97$. Adjusting for age and sex did not change any of the models. Mean clinician-rated depressive symptoms pretreatment was 21.87 ($SD = 4.61$) in ABFT and 21.92 ($SD = 4.07$) in TAU, mean posttreatment scores were 17.81 ($SD = 1.34$) in ABFT and 17.36 ($SD = 1.45$) in TAU.

Self-reported depressive symptoms were analysed through a set of mixed models. First, time was fitted as linear, squared or exponential fixed effect. The linear effect of time was the best fit for the data. Then fixed effect of treatment allocation and a treatment by time interaction term was added. There were no significant differences in rates of change in self-reported symptoms of depression between ABFT and TAU (table 3 and figure 3). The mean bi-weekly reduction in BDI-II score was - 0.94 (SE = 0.42) over the 16 weeks of treatment. The effect of treatment allocation and the interaction between time and treatment allocation were not significant. An independent samples t-test was performed to test if the number of sessions attended by the adolescent differed between ABFT and TAU. Adolescents in the ABFT treatment group ($M = 28.66$, $SD = 8.32$) received significantly more sessions than adolescents in the TAU condition ($M = 19.73$, $SD = 6.49$, $t[47.19] = 4.31$, $p = .001$).

Clinical significance

Fig. 2, the Brinley plot illustrates how individual adolescents scored pre- and posttreatment on clinician rated depressive symptoms. Only 16.6 % of the adolescents were rated as in the nonclinical range (GRID-HAMD < 15) at posttreatment, 63.3% adolescents remained relatively unchanged in the clinical range, and 16,6% adolescents were rated as having more severe symptoms at the end of treatment.

Discussion

The findings of the present study indicated that ABFT was no more effective than usual care in the treatment of adolescents with depression. Both clinician-ratings and self-reports showed reductions in depressive symptoms from pre- to posttreatment, but there were no differences in the outcomes of the two treatment conditions. Only five out of 60 youth showed full clinical remission after 16 weeks of treatment, three in ABFT and two in TAU.

The lack of differences between ABFT and TAU is consistent with findings by Diamond and colleagues (21, 23) who reported no differences between ABFT and enhanced usual care or non-directive supportive treatment in terms for remission rate, clinical response or reduction of depressive symptom at the end of treatment. However, in their studies, the adolescents' reduction in depressive symptoms was clinically significant. In the present study, very few adolescents had achieved full remission at the end of treatment, and importantly, most of the participants showed only small improvements in their level of depressive symptoms and were still considered clinically depressed based on independent clinical ratings. Evaluations of other treatment approaches for adolescent depression suggest that remission and response rates vary greatly. Following 12 to 16 weeks of treatment, between 35% and 65% of depressed adolescents fully recover (11, 44-46). Further, the lack of improvement for adolescents receiving TAU observed in the present study, is consistent with the extant literature (47, 48), which indicates that the majority of adolescents seen by specialist mental health services (receiving TAU), make little or no measurable improvement on any indicator of individual level-change. Taken together, these findings suggest that depression in adolescents is hard to treat and there is a continued need for improving treatment efficacy.

There may be several possible explanations for the observed low treatment response in the present study. A duration of 12 to 16 weeks of treatment is a common dosage of

Treatment of Depression in Adolescents

treatment in treatment evaluations. Studies evaluating CBT, IPT or a combination of CBT and Fluoxetine, with the same treatment duration have found these treatment approaches to be more effective than TAU and other active control conditions for adolescents with depression (11, 45, 49, 50), suggesting that it is reasonable to expect clinical improvement following 16 weeks of treatment.

One factor that has been associated with better treatment outcome in previous research is the number of therapy sessions per week (51). In the present study, adolescents in the TAU group received considerably fewer treatment sessions than adolescents in the ABFT group, within the same time frame. This would lead us to expect to observe a greater indication of improvement after 16 weeks of ABFT than what we found. An obvious possible interpretation may be that ABFT is simply not a more effective treatment for adolescent depression compared to standard care. Our sample was comparable to samples in other trials in terms of severity of depressive symptoms, comorbidity or on any other important factors (11, 21, 23). Differences in depressive symptoms going in to treatment cannot, therefore, explain the lack of improvement at the end of treatment.

Depressive disorders are hetrogenic, and the underlying mechanisms of depression may vary greatly among adolescents. A manualized therapy, focusing on relational bonds may not be suitable for everyone. ABFT targets conflicts between adolescents and their parents specifically, as well as attachment ruptures, and works well on resolving issues around such problems (52). ABFT may thus be more suitable for adolescents whose depressive disorder is related to problems in the parent-adolescent relationship, and who experience conflicts and high level of stress in their families. However, empirical efforts to identify factors which may guide treatment selection have not yet provided any conclusive evidence (53). Given the large number of adolescents with depression who do not respond sufficiently to a first-line treatment, it is necessary with continued efforts to identify factors

Treatment of Depression in Adolescents

that may moderate the treatment effects. Another factor that may explain the lack of treatment response to ABFT is cultural differences. ABFT was developed in North-America and earlier evaluations have relied on samples consisting of adolescents with a somewhat different cultural background than adolescents in our study. Cultural adaptation of treatments is essential when implementing a new treatment (9). This issue may be particularly important in a treatment that focuses on family and relational bonds. Even though attachment patterns are considered universal, the way they are expressed may differ across cultures. A manualized treatment may be vulnerable to such cultural differences as the protocol typically suggests a way in which to discuss emotions and family relationships which may not generalize well beyond the culture of origin.

Demonstrating significant differences between active psychotherapy approaches in efficacy and effectiveness studies is difficult and often requires a large sample size. Head to head comparison of two treatments often results in no differences between treatment groups (8, 12, 54). Our results must be viewed in the context of the study limitations and strengths. First, our sample size was relatively small. The study was not adequately powered to detect small differences in effect size between the two active treatments. Prior to data collection a power analysis was conducted, but the target sample size was not achieved. However, it is important to note that the analyses did not indicate that the results would have been different with a larger sample size. Even though we used recommended methods for handling missing data and followed ITT principles, we cannot completely rule out that there is a degree of selective attrition which may have impacted our results. Third, ABFT was a new intervention to the clinics, and ABFT may thus be more susceptible to barriers to implementation. ABFT was implemented relatively shortly before the trial onset, while TAU had the advantage of being a well established practice at the clinics. Training of clinicians to adequately perform ABFT may need more time, supervision and practice than what was offered. Fidelity was not

Treatment of Depression in Adolescents

assessed, although the issue was addressed in supervision with the ABFT therapists. Without proper adherence measurement it is difficult to decide whether the method was used adequately by the therapists in the trial. The trial supervisor discussed implementation of the protocol with the developers, and reviewed recorded and live therapy sessions using the ABFT adherence measure. Despite several limitations of the present study, we emphasize the importance of reporting the results of this trial. This study has high external validity as it was conducted in general mental health services, with a clinically referred population and few exclusion criteria. Publication bias and over-representation of positive trials introduces bias into meta-analyses because critical data are not available to the field, which consequently misinforms researchers, clinicians and policymakers (55). Importantly, a failure to report less than ideal results can lead to inefficient treatments being implemented, negative findings needs to be transparent to give a clear picture of the research field.

Conclusion

In light of our finding that both ABFT and TAU only have relatively modest effects for youth depression, we suggest caution when implementing new methods without adequate evidence of effect. Further, very few adolescents achieved full remission at the end of treatment, most adolescents did not respond adequately to treatment. The general finding that neither treatment lead to more positive improvements for adolescents with depression is alarming and has implications for practice and policy, underscoring the continued need for further research on treatment options for adolescent depression.

List of abbreviations

MDD = Major Depressive Disorder

CBT = Cognitive Behavioural Therapy

IPT= Interpersonal therapy

Treatment of Depression in Adolescents

RCT = Randomized Controlled Trial

ABFT = Attachment Based Family Therapy

FE-NST = Family-Enhanced Nondirective Supportive Therapy

TAU = Treatment as Usual

CAMH = Child and Adolescent Mental Health Service

GRID-HAMD = GRID – Hamilton Depression Rating Scale

BDI-II = Beck Depression Inventory – II,

K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version

SIQ-JR = Suicidal Ideation Questionnaire – Junior

ITT = Intent – to – treat

IC = Information Criteria

References

1. Costello EJ, Maughan B. Annual Research Review: Optimal outcomes of child and adolescent mental illness. *Journal of Child Psychology and Psychiatry*. 2015;56(3):324-41.
2. Costello EJ, Egger H, Angold A. 10-Year Research Update Review: The Epidemiology of Child and Adolescent Psychiatric Disorders: I. Methods and Public Health Burden. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2005;44(10):972-86.
3. Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE. Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology*. 1998;107(1):128-40.
4. Lewinsohn PM, Rohde P, Klein DN, Seeley JR. Natural Course of Adolescent Major Depressive Disorder: I. Continuity Into Young Adulthood. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999;38(1):56-63.
5. WHO. Depression World Health Organization: World Health Organization; 2020 [updated January 30, 2020; cited 2020 February 20]. Available from: <https://www.who.int/news-room/fact-sheets/detail/depression>.
6. Hawton K, Saunders KEA, O'Connor RC. Self-harm and suicide in adolescents. *The Lancet*. 2012;379(9834):2373-82.
7. David-Ferdon C, Kaslow NJ. Evidence-Based Psychosocial Treatments for Child and Adolescent Depression. *Journal of Clinical Child & Adolescent Psychology*. 2008;37(1):62-104.
8. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: A meta-analysis. *Psychological Bulletin*. 2006;132(1):132-49.

Treatment of Depression in Adolescents

9. Weisz JR, Kuppens S, Eckshtain D, Ugueto AM, Hawley KM, Jensen-Doss A. Performance of evidence-based youth psychotherapies compared with usual clinical care: a multilevel meta-analysis. *JAMA psychiatry*. 2013;70(7):750-61.
10. Klein JB, Jacobs RH, Reinecke MA. Cognitive-Behavioral Therapy for Adolescent Depression: A Meta-Analytic Investigation of Changes in Effect-Size Estimates. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007;46(11):1403-13.
11. Mufson L, Dorta KP, Wickramaratne P, Nomura Y, Olfson M, Weissman MM. A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry*. 2004;61(6):577-84.
12. Rosselló J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *Journal of Consulting and Clinical Psychology*. 1999;67(5):734-45.
13. Mychailyszyn MP, Elson DM. Working through the blues: A meta-analysis on Interpersonal Psychotherapy for depressed adolescents (IPT-A). *Children and Youth Services Review*. 2018;87:123-9.
14. Pu J, Zhou X, Liu L, Zhang Y, Yang L, Yuan S, et al. Efficacy and acceptability of interpersonal psychotherapy for depression in adolescents: A meta-analysis of randomized controlled trials. *Psychiatry Research*. 2017;253:226-32.
15. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *The Lancet*. 2012;379(9820):1056-67.
16. Brent DA, Holder D, Kolko D, Birmaher B, Baugher M, Roth C, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. *Arch Gen Psychiatry*. 1997;54(9):877-85.

Treatment of Depression in Adolescents

17. Birmaher B, Brent DA, Kolko D, Baugher M, Bridge J, Holder D, et al. Clinical outcome after short-term psychotherapy for adolescents with major depressive disorder. *Arch Gen Psychiatry*. 2000;57(1):29-36.
18. Watanabe N, Hunot V, Omori IM, Churchill R, Furukawa TA. Psychotherapy for depression among children and adolescents: a systematic review. *Acta Psychiatrica Scandinavica*. 2007;116(2):84-95.
19. Sander JB, McCarty CA. Youth Depression in the Family Context: Familial Risk Factors and Models of Treatment. *Clinical Child and Family Psychology Review*. 2005;8(3):203-19.
20. Helsen M, Vollebergh W, Meeus W. Social Support from Parents and Friends and Emotional Problems in Adolescence. *Journal of Youth and Adolescence*. 2000;29(3):319-35.
21. Diamond GS, Kobak RR, Krauthamer Ewing ES, Levy SA, Herres JL, Russon JM, et al. A Randomized-Controlled Trial: Attachment-Based Family and Nondirective Supportive Treatments for Suicidal Youth. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2018.
22. Diamond GS, Reis BF, Diamond GM, Siqueland L, Isaacs L. Attachment-Based Family Therapy for Depressed Adolescents: A Treatment Development Study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002;41(10):1190-6.
23. Diamond GS, Wintersteen MB, Brown GK, Diamond GM, Gallop R, Shelef K, et al. Attachment-Based Family Therapy for Adolescents with Suicidal Ideation: A Randomized Controlled Trial. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2010;49(2):122-31.
24. Israel P, Diamond G. Feasibility of Attachment Based Family Therapy for depressed clinic-referred Norwegian adolescents 2012.

25. Williams JB, Kobak KA, Bech P, Engelhardt N, Evans K, Lipsitz J, et al. The GRID-HAMD: standardization of the Hamilton Depression Rating Scale. *International Clinical Psychopharmacology*. 2008;23(3):120-9.
26. Achenbach TM. Manual for the youth self-report and 1991 profile. Burlington: Department of Psychiatry, University of Vermont; 1991.
27. Eimecke SD, Remschmidt H, Mattejat F. Utility of the Child Behavior Checklist in screening depressive disorders within clinical samples. *Journal of Affective Disorders*. 2011;129(1-3):191-7.
28. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(7):980-8.
29. CheckWare. CheckWare Assessment Systems: CheckWare AS; 2013 - 2016 [cited 2020 February 10th]. Available from: www.checkware.com.
30. Tabuse H, Kalali A, Azuma H, Ozaki N, Iwata N, Naitoh H, et al. The new GRID Hamilton Rating Scale for Depression demonstrates excellent inter-rater reliability for inexperienced and experienced raters before and after training. *Psychiatry Research*. 2007;153(1):61-7.
31. Zimmerman M, Morgan TA, Stanton K. The severity of psychiatric disorders. *World psychiatry : official journal of the World Psychiatric Association (WPA)*. 2018;17(3):258-75.
32. Enders CK. *Applied Missing Data Analysis*. New York: The Guilford Press; 2010.
33. Van Buuren S. *Flexible imputation of missing data*. New York: Chapman and Hall/CRC; 2018. Available from: <https://stefvanbuuren.name/fimd/>.
34. Enders CK. Multiple imputation as a flexible tool for missing data handling in clinical research. *Behaviour Research and Therapy*. 2017;98:4-18.

35. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.
36. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*. 2011;45(3).
37. RStudio Team. RStudio: Integrated Development for R. Boston, MA: RStudio, Inc.; 2016.
38. Gottschall AC, West SG, Enders CK. A Comparison of Item-Level and Scale-Level Multiple Imputation for Questionnaire Batteries. *Multivariate Behavioral Research*. 2012;47(1):1-25.
39. Eekhout I, de Vet HC, de Boer MR, Twisk JW, Heymans MW. Passive imputation and parcel summaries are both valid to handle missing items in studies with many multi-item scales. *Statistical methods in medical research*. 2018;27(4):1128-40.
40. Reynolds WM. SIQ, Suicidal ideation questionnaire: Professional manual: Psychological Assessment Resources; 1988.
41. Gaffert P, Meinfelder F, V. B. Towards an MI-proper Predictive Mean Matching. [Discussion Paper]. In press 2015.
42. Blampied NM. Analyzing Therapeutic Change Using Modified Brinley Plots: History, Construction, and Interpretation. *Behav Ther*. 2017;48(1):115-27.
43. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015;67(1):1-48.
44. 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 Study (TADS). *Journal of the American Academy of Child & Adolescent Psychiatry*. 2006;45(12):1404-11.

Treatment of Depression in Adolescents

45. Brent DA, Holder D, Kolko D, Birmaher B, Baugher M, Roth C, et al. A Clinical Psychotherapy Trial for Adolescent Depression Comparing Cognitive, Family, and Supportive Therapy. *JAMA Psychiatry*. 1997;54(9):877-85.
46. McCarty C, Weisz J. Effects of Psychotherapy for Depression in Children and Adolescents: What We Can (and Can't) Learn from Meta-Analysis and Component Profiling. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2007;46:879-86.
47. Smith AM, Jensen-Doss A. Youth psychotherapy outcomes in usual care and predictors of outcome group membership. *Psychological Services*. 2017;14(1):66-76.
48. Bear HA, Edbrooke-Childs J, Norton S, Krause KR, Wolpert M. Systematic Review and Meta-analysis: Outcomes of Routine Specialist Mental Health Care for Young People With Depression and/or Anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2019.
49. 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. *BMJ*. 2007;335(7611):142.
50. March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *Jama*. 2004;292(7):807-20.
51. Cuijpers P, Huibers M, Daniel Ebert D, Koole SL, Andersson G. How much psychotherapy is needed to treat depression? A metaregression analysis. *Journal of Affective Disorders*. 2013;149(1):1-13.
52. Diamond GS, Russon J, Levy S. Attachment-Based Family Therapy: A Review of the Empirical Support2016.

53. Gunlicks-Stoessel M, Eckshtain D, Lee S, Reigstad K, Mufson L, Weisz J. Latent Profiles of Cognitive and Interpersonal Risk Factors for Adolescent Depression and Implications for Personalized Treatment. *Journal of Abnormal Child Psychology*. 2019.
54. Weisz JR, Southam-Gerow MA, Gordis EB, Connor-Smith JK, Chu BC, Langer DA, et al. Cognitive-behavioral therapy versus usual clinical care for youth depression: An initial test of transportability to community clinics and clinicians. *Journal of Consulting and Clinical Psychology*. 2009;77(3):383-96.
55. Cuijpers P, Smit F, Bohlmeijer E, Hollon SD, Andersson G. Efficacy of cognitive-behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. *British Journal of Psychiatry*. 2018;196(3):173-8.

Treatment of Depression in Adolescents

Table 1. Baseline Demographic and Diagnostic Data in adolescents (N=60) allocated to Attachment Based Family Therapy or Treatment as Usual

Variable		Treatment condition	
		ABFT (n=30)	TAU (n=30)
Age, years (SE)		15.03 (1.35)	14.77 (1.36)
Gender, % (n)	Female	90 (27)	83.3 (25)
Dropout, % (n)	Excluded	7 (2)	3.3 (1)
	Drop out	10 (3)	13.3 (4)
Ethnicity, % (n)	Norwegian	100 (30)	96.7 (30)
	Skandinavian other than Norwegian	0 (0)	3.3 (1)
Living with, % (n)	Both parents	29.6 (8)	36.7 (11)
	Two home family	18.5 (5)	13.3 (4)
	Father (and partner)	18.5 (5)	13.3 (4)
	Mother (and partner)	33.3 (9)	33.3 (10)
	Other	0 (0)	3.3 (1)
Psychiatric comorbidity, % (n)	Dysthymia	3.3 (1)	0 (0)
	Any anxiety disorders ^a	43.3 (13)	46.7 (14)
	Obsessive-Compulsive Disorder	6.7 (2)	6.7 (2)
	Externalizing disorder	0 (0)	13.4 (4)
	PTSD	3.3 (1)	3.3 (1)
	Enuresis	3.3 (1)	6.7 (2)
	No comorbidity	53.3 (16)	46.7 (14)
Depressive symptoms, mean (SD)	BDI-II	34.23 (7.34)	36.21 (9.84)
	GRID- HAMD	21.87 (4.61)	21.92 (4.07)

Note: BDI-II = Beck Depression Inventory II, GRID-HAMD = GRID-Hamilton Depression Rating Scale,

^aIncludes social phobia, specific phobia, agoraphobia, generalized anxiety disorder, anxiety disorder NOS, obsessive compulsive disorder.

^bIncludes oppositional defiant disorder, attention deficit/hyperactivity disorder.

Table 2. Linear Mixed model of depressive symptoms measured by GRID-HAMD at week 16.

	Null Model					Model 1				Model 2			
Fixed effect	β	CI	t	p	B	CI	t	p	β	CI	t	p	
Intercept	19.71	(18.41, 21.01)	30.05	-	21.83	(20.26, 23.41)	27.40	-	21.80	(19.55, 24.05)	19.20	0.00	
Time					-4.25	(-6.43, -2.07)	90.29	-	-4.44	(-7.62, -1.25)	-2.77	0.01*	
ABFT									0.07	(-3.11, 3.25)	0.04	0.97	
ABFT:Time									0.38	(-3.96, 4.71)	0.17	0.86	
Model comparison – Wald													
Model 1 vs. Null model											0.0001*		
Model 2 vs. 3											0.98		

Note: ABFT = Attachment Based Family therapy, GRID-HAMD = GRID-Hamilton Depression Rating Scale

Treatment of Depression in Adolescents

Table 3: Linear Mixed Model of self-reported depressive symptoms measured at baseline and after 2, 4, 6, 8, 10, 12, 14,16 weeks of the treatment.

	Null Model		Model 1		Model 2	
Fixed effect	β	CI	β	CI	β	CI
Intercept	32.07	(29.41, 34.75)	34.64	(32.46, 36.81)	34.67	(31.58, 37.77)
Time			-1.017	(-1.62, -0.42)	-0.94	(-1.81, -0.09)
ABFT					-0.07	(-4.41, 4.28)
ABFT:time					-0.144	(-1.35, 1.05)
Random effects						
$\sigma^2_{\text{Intercept}}$		83,98		41,35		41,35
σ^2_{Time}				1,85		1,85
Residual		7,71		6,4		6,4
Model inf.						
AIC		1608.08		1561.40		1565.34
BIC		1618.22		1581.68		1592.38
Log-Likelihood		-801.04		-774.70		-774.67
χ^2 (df)				52.67 (3)		0.06 (2)
Pr(>Chisq)				<0.001 ***		0.97

Note: Self reported depressive symptoms measured by Beck Depression Inventory-II, ABFT = Attachment

Based Family therapy

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flowchart of participants comparing Attachment Based Family Therapy (ABFT) with Treatment as Usual (TAU)

Note: BDI-II = Beck Depression Inventory – II, GRID-HAMD = GRID – Hamilton Depression Rating Scale

Figure 2. Modified Brinley Plot, a scatter plot to visualise individual change on clinician rated depressive symptoms from before and after therapy.

Note. When there are no differences pre-and post- treatment scores on GRID-Hamilton Depression Rating Scale (GRID-HAMD), data points are aligned on the 45° line. Points above this line represent depression scores that are higher at week 16 than at baseline (and reversely for points below the 45° line). The shaded symbols represent the uncertainty of the imputed scores. The dashed lines represents clinical cut off points for remission and response.

Treatment of Depression in Adolescents

Figure 3. Self- reported depressive symptoms by treatment at baseline and after 2, 4, 6, 8, 10, 12, 14,16 weeks of of treatment.

Note: BDI-II = Beck Depression Inventory – II. TAU = Treatment at Usual, ABFT = Attachment

Based Family Therapy.