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Moderation of treatment effects by parent-adolescent conflict in a randomised controlled trial of Attachment-Based Family Therapy for adolescent depression

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Abstract

Background: Conflict with parents is frequent in adolescent depression, and has been shown to predict poor treatment outcomes. Attachment Based Family Therapy (ABFT) is a manualised treatment for adolescent depression that may be robust to parent-adolescent conflict.
Objective: To evaluate the hypothesis that parent-adolescent conflict moderates the outcome of Attachment-Based Family Therapy compared with treatment as usual.
Methods: Data were obtained from a randomised trial comparing 16 weeks of ABFT to treatment as usual, in Norwegian Child and Adolescent Mental Health Services. Sixty adolescents with moderate to severe depression and their parents were recruited. Change in Grid-Hamilton Depression Rating Scale scores from baseline to week 16 was modelled using linear mixed models, and a three-way interaction of time, treatment allocation and a continuous measure of parent-adolescent conflict was fitted to estimate a moderator effect. The moderator model was compared to simpler models using leave-one-out cross-validation.
Results: Better outcomes were predicted for Attachment-Based Family Therapy at high levels of mother-adolescent conflict, and for treatment as usual at low levels of mother-adolescent conflict, giving preliminary support to the moderator hypothesis. Findings for father-adolescent conflict were mixed. Cross-validation did not clearly support the moderator model over a simple effect of time, indicating that the replicability of these findings is uncertain.
Conclusion: The results suggest that parent-adolescent conflict should be further studied as a moderator of outcome in Attachment-Based Family Therapy. The trial did not meet its recruitment target and had high attrition, limiting the conclusions that may be drawn.

Keywords: Attachment-Based Family Therapy; adolescent depression; randomised controlled trial; moderator; parent-adolescent conflict; Bayesian data analysis

Introduction

Adolescents who suffer from depression report experiencing more conflict and less support in the relationship with their parents (1). The transition into adolescence is normatively accompanied by increases in parent-child conflict (2), but not all parent-adolescent dyads manage these conflicts equally well (3). Parent-adolescent conflict has been linked to onset of adolescent depressive symptoms in multiple studies (4-6). Parent-adolescent conflict has further been found to predict recurrence of depression in adulthood (7), and depression has been found to mediate intergenerational continuity in high-conflict family environments (8).

Parent-adolescent conflict and treatment of adolescent depression

Because parent-adolescent conflict has shown a consistent association with the development and course of adolescent depression, it has also been studied as a potential predictor or moderator of outcome in multiple clinical trials of adolescent depression treatments. Moderators in the context of clinical trials have been defined as baseline variables

across which the effect of treatment allocation on treatment outcome varies. Baseline variables that are associated with treatment outcome independently of treatment allocation are referred to as non-specific predictors (9).

Adolescent-reported parent-adolescent conflict was found to be a non-specific predictor of both treatment nonresponse and depression recurrence in a trial of different psychotherapies for adolescent depression (10). In the *Treatment of Selective Serotonin Reuptake Inhibitor-Resistant Depression in Adolescents Study*, adolescent report of more parent-adolescent conflict was also found to be a non-specific predictor of nonresponse (11). Mother-report of frequent and intense conflict was similarly found to be a non-specific predictor of poor outcomes in an exploratory analysis of data from the *Treatment of Adolescent Depression Study* (12).

However, in a trial comparing Interpersonal Therapy to treatment as usual, adolescents reporting more conflict with mothers at baseline benefited more from Interpersonal Therapy, which is a moderator effect (13). Similarly, in a preventive group intervention based on Interpersonal Therapy with school counselling, the intervention was superior to school counselling only for those adolescents who reported heightened parent-adolescent conflict (14), also showing moderation by parent-adolescent conflict for the interpersonally focused treatment. Another comparable finding was reported from a trial comparing family-focused treatment to enhanced usual care for adolescents with a bipolar disorder (15). For adolescents from families reporting heightened expressed emotion, the family focused treatment was superior to enhanced usual care, but this was not the case for adolescents from families with lower levels of expressed emotion. Seen together, these findings suggest that while parent-adolescent conflict can impede treatment, treatments gains can perhaps be made in these cases by focusing treatment on family-related issues, making treatment effectiveness conditional on the level of conflict or family distress.

Attachment Based Family Therapy for adolescent depression

Attachment-Based Family Therapy (ABFT) is a manualised family therapy for adolescent depressive symptoms and suicidal ideation (16). ABFT initially focuses on identification and repair of relational ruptures between depressed adolescents and their parents. Building on reduced conflict and renewed trust in the parent-adolescent relationship, the family is then guided in collaborative work to reduce depressive symptoms and improve functioning. The developers of the intervention have conducted several clinical trials and other program evaluations (17), and ABFT has been designated a probably efficacious treatment (18). Still, in the largest randomised controlled trial conducted to date, ABFT was not found to be superior to family-enhanced non-directive supportive therapy for reducing adolescent suicidal ideation (19). A secondary analysis of that trial found that observations of less cooperative family communication, as well as non-white race and lower income-to-needs ratio predicted higher treatment benefit in both trial arms (20).

In Norway, an initial study found ABFT implementation in Norwegian public child and adolescent mental health services to be feasible and the treatment to be acceptable to Norwegian families (21). A larger Norwegian randomised controlled trial comparing 16 weeks of ABFT to treatment as usual (TAU) for adolescent depression (clinicaltrials.gov identifier NCT01830088) was conducted to follow up on these findings. Contrary to the primary hypothesis of the trial, ABFT was not found to be superior to treatment as usual (22). While the findings from these recent trials do not provide evidence that ABFT on average is more effective than treatment as usual or other active comparisons in treating adolescent depression or suicidal ideation, ABFT is a treatment where moderation of effectiveness by parent-adolescent conflict is highly plausible. In line with this, we evaluate the moderator hypothesis that the difference in outcome between ABFT and treatment as usual would be larger at higher levels of parent-adolescent conflict and in favour of ABFT.

Methods

We analyse baseline and outcome data from the Norwegian two-arm randomised effectiveness trial comparing ABFT to TAU (22). Moderation is defined as an effect of treatment allocation that is conditional on a baseline variable, in this case parent-adolescent conflict (9).

Participants

Participating families were recruited among adolescents referred to two Child and Adolescent Mental Health Services (CAMHS) in Southe-Eastern Norway. The clinics were publicly funded, and all treatments were provided free of charge to the patients and their families, within the framework of the universal health insurance system of Norway. During pre-specified recruitment periods, all referral letters for adolescents (13 - 17 years) were examined for mentions of depression or core depressive symptoms (depressed mood, anhedonia, or fatigue). The CAMHS routinely administered the Youth Self Report (23), and these were screened for raw scores on the Affective Problems subscale above 6 to find depressed adolescents not identified as such in their referral letters (24). Eligible adolescents or their

parents, depending on adolescent age, were contacted by telephone and invited to participate in a randomised trial of family therapy for adolescent depression. Participants were required to be currently living with an adult who had become a caregiver for them before age four, and willing to have this adult participate in treatment. Interested adolescents meeting these criteria were screened with Beck Depression Inventory-II (25) over telephone and invited for an assessment session if they scored above 17, a threshold expected to maximise sensitivity (26). Adolescents were included in the study if they scored above 15 on the Grid Hamilton Depression Rating scale (GRID-HAMD, 27) and met diagnostic criteria for a current Major Depressive Disorder (28). Adolescents meeting criteria for a psychotic disorder, anorexia nervosa, bipolar disorder, intellectual disability or pervasive developmental disorder were excluded from the study. In a small number of cases, exclusionary criteria (psychotic disorder or atypical anorexia nervosa) were not detected at baseline but uncovered during treatment. One family withdrew consent shortly after randomisation and are not included in any analyses. Sixty participants were randomised, of which 52 (87%) were female. Figure 1 shows the flow of participants through the study.

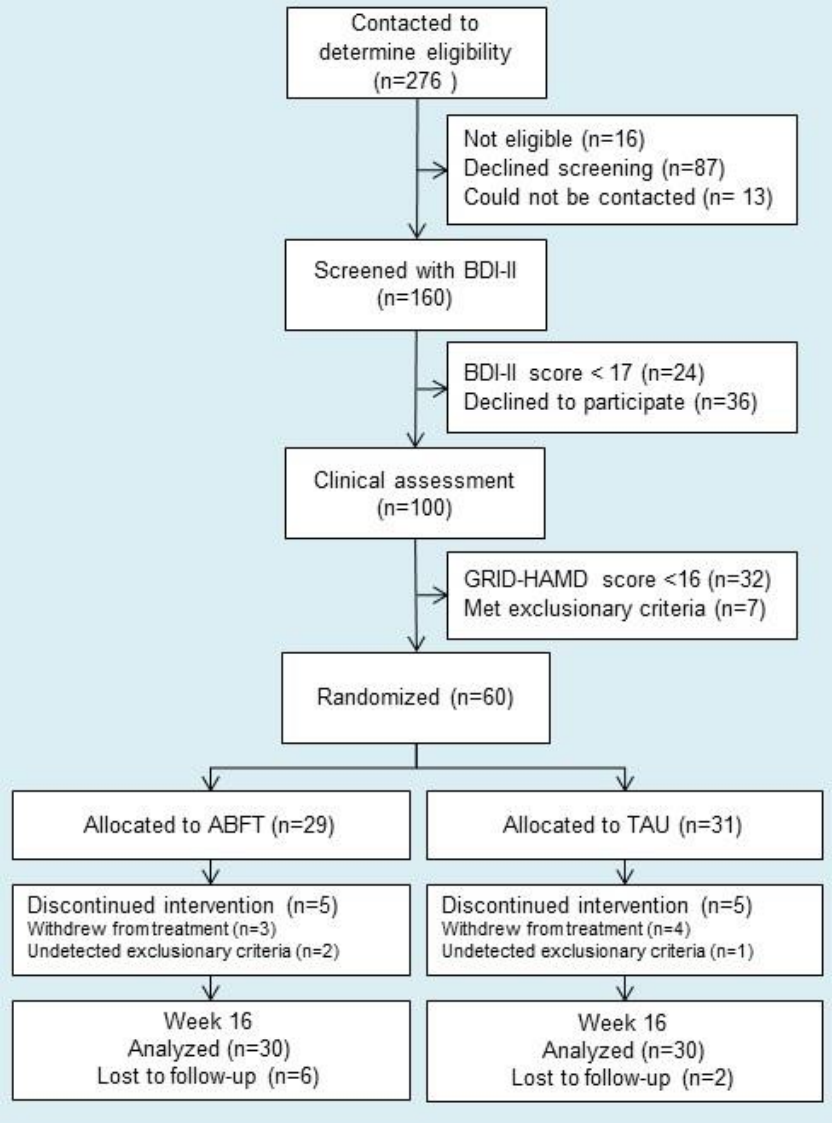

FIGURE 1. CONSORT flow-chart for study participants

Procedures

Participating adolescents and their parents met with a study-affiliated clinical psychologist (the first or second author) at the CAMHS and written informed parental consent and adolescent assent was obtained. Adolescents and parents were then interviewed separately with the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version (K-SADS-PL, 29), and the depressive symptoms of the adolescent were further assessed with the GRID-HAMD (27). All interviews were video-recorded. Both parents and adolescents completed self-report measures of parent-adolescent conflict before randomisation. If the adolescent met inclusion criteria, the assessing clinician conducted randomisation by opening a sealed, numbered envelope containing the treatment allocation. Randomisation was stratified by site, age (13-15 years and 16-17 years), gender (male and female), and severity of depression (GRID-HAMD score of ≤ 24 and ≥ 25). 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 and the adolescent concerning the assessment and implemented standard safety monitoring procedures to the extent deemed necessary. CAMHS staff were then informed of treatment allocation and given a report of the assessment findings. Treatment outcome was assessed at 16 weeks after randomisation by an independent clinical psychologist blinded to treatment allocation.

Treatment

Both ABFT and TAU were provided for a minimum of 16 weeks but could be extended if deemed necessary by the therapist. ABFT consisted of weekly sessions as well as extra parent sessions in the early part of therapy. ABFT was delivered according to an available draft of the treatment manual (16). TAU was not manualised, and the therapists were free to provide the treatment they considered most appropriate. Adolescents allocated to ABFT on average received a higher number of sessions than those allocated to TAU, although some sessions in ABFT are conducted with parents alone. The mean number of sessions was 28.66 (SD 8.32) in ABFT, and 19.73 (SD 6.49) in TAU. When trial measurements or assessments indicated that adolescents were at high risk of self-harm or suicide, the therapist assigned to the case was immediately notified by study staff.

Clinician training and supervision

Clinicians were trained in ABFT for the purpose of the trial. Training consisted of a day-long introductory seminar, followed by a three-day workshop, as well as reading the treatment manual. Clinicians providing ABFT were required to have completed one case of ABFT under supervision before treating patients allocated to ABFT in the trial. All ABFT sessions were videotaped for supervision purposes. Weekly supervision by an experienced ABFT therapist was intended, but not achieved in practice. For the duration of the trial, the clinicians in the ABFT arm met nearly weekly and did peer supervision, and 42% of these sessions were also attended by a certified ABFT therapist and trainer. Clinicians in the TAU arm were also recruited from the regular staff of the CAMHS, and treated patients in the trial as part of their regular patient workload. None of the ABFT therapists treated patients allocated to TAU. Access to supervision for clinicians providing TAU varied by clinical experience, but all had access to discussing cases in multidisciplinary teams. Most of the clinicians across both treatment arms were trained as clinical psychologists (>75%), but there were also a small number of clinical social workers, clinical pedagogues and medical doctors in resident training providing treatment.

Changes to the protocol

According to the protocol registered in clinicaltrials.gov (NCT01830088), our primary and secondary outcome measures were supposed to be collected at 12, 24 and 48 weeks after treatment start. A four week waiting period from randomisation to treatment start was planned, but this was not feasible due to the severity of the depression for many patients and Norwegian standards of care. Consequently, the treatment period was extended from 12 to 16 weeks, but the time from randomisation to outcome assessment was unchanged.

Measures

Diagnosis

Diagnostic evaluations were conducted with the K-SADS-PL (29). Interrater reliability of the diagnosis of Major Depressive Disorder was established by an independent clinician conducting a blinded rescoring of a subsample of 28 videorecorded interviews, including both excluded and included patients. κ for current Major Depression was 0.56, indicating fair interrater reliability (30).

Treatment outcome

The primary outcome measure of the clinical trial was the total score on the GRID-HAMD, which is a version of the Hamilton Rating Scale for Depression that includes a structured interview guide, and scoring guidelines for weighing severity and frequency of symptoms to a composite score (27).

The GRID-HAMD has previously shown excellent interrater reliability (31). Interrater reliability was assessed in the same way as for diagnoses, with the same subsample. The two-way mixed, consistency, average-measures intraclass correlation coefficient for the total score (32) was 0.89, indicating good interrater reliability.

Parent-adolescent conflict

Parent-adolescent conflict was measured with the Perception of the Dyad subscale of the Conflict Behavior Questionnaire (CBQ, 33). This scale consists of 16 items rated true or false concerning the current state of conflict in a parent-adolescent relationship, and was completed by parents as well as the adolescents separately for each parent. Example items are "My [parent/child] and I speak to each other only when we have to", "At least once a day we get angry at each other" and "We have enjoyable talks at least once a day" (reverse scored). The CBQ was translated to Norwegian for this study, and a blind reverse translation was approved by the original author.

Analysis plan

Analyses included all patients randomised to treatment regardless of adherence to study treatment or procedures, in accordance with intent-to-treat principles. One patient withdrew consent and was omitted from all analyses. We conducted analysis within a Bayesian modelling framework, with estimation by Hamiltonian Monte Carlo as implemented in the statistical modelling platform Stan, using the RStan package (version 2.19.2, 34) for R (version 3.6.1, 35). The results of a Bayesian analysis are distributions that show the probability of different model parameter values, conditional on the data and the model. For readers unfamiliar with Bayesian statistics, Baldwin and Larson (36) provide a very accessible introduction to the use of Bayesian linear regression in clinical psychology.

Analysing a multi-informant measure of conflict

To improve the measurement precision of the hypothesised moderator variable we used a latent variable rather than raw scores, which we obtained by fitting a two-parameter logistic item response model to the CBQ data. The Stan platform is well suited for estimating IRT models, which can be embedded in a larger model of interest (37). Adolescents completed the CBQ separately for each parent, and each parent completed the CBQ for their relationship to the adolescent. In the majority of cases this gave four different ratings of the degree of parent-adolescent conflict, two by the adolescent for each parent, and one by each parent. We chose to model all four ratings as potential moderators, fitting these models separately. We used the report of all four informants to fit the item response model, specifying the four latent conflict variables to have a multivariate normal distribution, with means of 0 and standard deviations of 1, and constraining item parameters to be equal across informants. Checking this assumption of measurement invariance (38) resulted in removal of two items. Visual inspection of the posterior distributions of item characteristic curves plotted against the data indicated good fit for the remaining items. These plots as well as further details concerning checking of measurement invariance are available online at DOI: 10.17605/OSF.IO/KPJC6.

Robust modelling of treatment moderation

We specified a hierarchical linear regression model with pre- and post-treatment GRID-HAMD scores nested within patients as the outcome variable, and a random intercept for each patient. The model included terms for the predictor variables time, treatment allocation and parent-adolescent conflict, and interaction terms for treatment by time, conflict by time and a three-way interaction of treatment by conflict by time. The three-way interaction estimates the moderator effect of interest, while the conflict by time interaction estimates a non-specific predictor effect. Treatment allocation was coded as -0.5 for treatment as usual and +0.5 for ABFT, which allows the coefficients for treatment or interactions with treatment to be interpreted as the predicted difference between the treatment groups, with the sign indicating the direction of the difference (9). We standardised the GRID-HAMD scores by subtracting the median score across both time points of 21 and dividing by two times the median absolute deviation of 8, as standardisation can improve Hamiltonian Monte Carlo estimation and simplifies specification of reasonable priors (37).

Regression models with normally distributed errors are sensitive to outliers (39). Psychotherapy outcome is known to be influenced strongly by extratherapeutic factors (40), which increases the probability of having multivariate outliers. To avoid having outliers influencing slope estimates disproportionally to the bulk of observations we specified a Students' t-distribution with five degrees of freedom to the errors, giving a robust estimation of regression coefficients (37, 41).

After fitting the model, we used exact leave-one-out cross-validation (LOO-CV), leaving out one patient at a time, to compare the model to three less complex models, repeating this across all four informant perspectives on conflict. LOO-CV estimates the expected log posterior density (ELPD), indicating how well the model is expected to fit new data from the same distribution (42). The first of

these three models had the term for the moderator effect removed, making it a model with conflict as a non-specific predictor of outcome. The second had all terms involving conflict removed, making it a model of different effects of treatment allocation over time. The third had all terms involving both conflict and treatment removed, making it a model of the effect of time alone. For clarity, we will term these four models "Moderator", "Non-specific predictor", "Treatment" and "Time" when comparing them.

Missing data management

There was a substantial number of patients missing outcome data (38%). In most cases, outcome data was missing due to adolescents declining to come for assessment sessions or not showing up for such sessions, as well as lacking resources and administrative capacity to follow up further in such cases. Bayesian data analysis provides a natural way to handle such missing observations, by estimating these as unobserved parameters of the model, which ensures that the loss of information due to missing data is reflected in the posterior distribution as increased uncertainty of model parameters such as regression coefficients (43). When single items were missing from the CBQ, we estimated the latent variable of the IRT model from the observed items. In some cases, the entire CBQ was missing, and in these cases the latent variable was also estimated as a model parameter. This applied to 12% of adolescent reports of conflict with father, 28% of father reports of conflict, 3% of adolescent report of conflict with mother and 5% of mother reports of conflict. In some cases of missing reports of father-adolescent conflict, this was due to fathers not participating in treatment.

Prior distributions

In a Bayesian data analysis, a prior distribution must be assigned to all model parameters, representing our prior knowledge of these parameters. This prior distribution is combined with the likelihood of the data to produce the posterior distribution of the parameters. This allows us to include information and assumptions on what ranges of a parameter are at all reasonable. When reading the results of a Bayesian data analysis, the reader should examine the prior distributions used and assess whether they are reasonable assumptions, and these should hence always be reported. The prior distributions used in this analysis and their justifications are summarised in Table 1.

TABLE 1. Prior distributions and reasoning for choices of prior

Parameter	Prior Distribution	Reasoning
Regression coefficients	Normal (0, 1)	Weakly informative prior as the dependent variable is centred on the median score and scaled by twice the median absolute deviation
Error variance	Half-student's t (3, 0, 1)	Weakly informative prior on the error variance, putting most of the prior weight on errors between 0 and 1, but with heavy tails allowing for a much higher error variance
Random intercepts	Hierarchical normal prior, with location 0 and a Half-student's t (3, 0, 1) prior on the scale.	Defines random intercepts as deviations from the intercept of the whole sample, and estimates the variance of the random intercepts from the data, with a weakly informative hyperprior
Latent variables for CBQ IRT model	Multivariate normal (0, 1) with an LKJ (2) prior on the standardised covariance matrix	Defines the latent variables for parent-adolescent conflict as four correlated Normal (0, 1) variables with a weakly informative prior on the correlation coefficients
Item thresholds for CBQ IRT model	Hierarchical normal prior with hyperpriors Normal (0, 3) for location and Half-students' t (3, 0 ,1) for scale	Weakly informative hierarchical prior for the item thresholds, as these are interdependent with the defined latent variable
Item discrimination for CBQ IRT model	Gamma (2, 0.5)	Places most of the prior weight on discrimination between 1 and 5, which is the most probable range for items of an established instrument, but does not rule out higher or lower values

Model fitting and validation of convergence

We fitted all models using four chains with the default Stan algorithm, 1000 warmup iterations and drawing 3500 samples from each chain. Gelman-Rubin statistics ($\hat{R}$) were below 1.01 for all parameters. Other Stan convergence diagnostics also indicated convergence for all chains and valid sampling from the posterior.

Results

Table 2 contains descriptive information about the sample. Table 3 summarises posterior estimates from the moderator model with the different informants.

The coefficient for the three-way interaction between treatment, time and parent-adolescent conflict is interpretable as the predicted difference in outcome (in units of 8 points on the GRID-HAMD) between ABFT and treatment as usual associated with a level of parent-adolescent conflict one standard deviation above the sample mean. The sign of the coefficient signifies the direction of the difference, with a negative coefficient being a difference favouring ABFT when conflict increases.

TABLE 2. Sample characteristics

Variable		Treatment arm	
		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)
	Dropped out	10 (3)	13.3 (4)
Ethnicity, % (n)	Norwegian	100 (30)	96.7 (30)
	Scandinavian	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 any new partner)	18.5 (5)	13.3 (4)
	Mother (and any new partner)	33.3 (9)	33.3 (10)
	Other	0 (0)	3.3 (1)
Psychiatric comorbidity, % (n)	Dysthymia	3.3 (1)	0 (0)
	Any anxiety disorder	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 Score; GRID-HAMD = Grid-Hamilton Depression Rating Scale Score; Any anxiety disorder includes social phobia, specific phobia, agoraphobia, generalized anxiety disorder, anxiety disorder NOS and obsessive compulsive disorder; Externalising disorder includes oppositional defiant disorder and attention deficit/hyperactivity disorder.

We report the 66% and 90% Highest Density Intervals (44) of the marginal posterior distributions of each parameter. The choice of intervals is arbitrary, but .66 and .90 correspond to probabilities that have been described as likely and very likely, respectively (45). These intervals show that there is considerable uncertainty, in particular for the coefficient for the moderator effect, and these data do not completely rule out an effect close to 0. Still, the main weight of the evidence is on a difference between ABFT and treatment as usual in the expected direction for three of the informants. The posterior probabilities of a coefficient for the moderator effect below 0 is .98 for adolescent report of conflict with mother, .50 for adolescent report of conflict with father, .97 for mother report of conflict and .97 for father report of conflict. Correlations between the latent conflict variables of the different informants are summarised in Table 4.

Visualised model predictions

To understand the implications of a fitted model, plotting its predictions across the range of a predictor variable can be helpful. Figure 2 shows the predicted change in GRID-HAMD score from baseline to outcome across the range of parent-adolescent conflict for all four informants, with the different lines representing the two treatment conditions (red for ABFT and black for treatment as usual). The uncertainty of the prediction is visualised by shading showing the 90% HDI. The points are the observations used to fit the model.

Given the uncertainty in these estimates, they must be interpreted cautiously. For conflict with mother, the pattern is similar for both adolescent and mother report, with better outcomes predicted for ABFT relative to treatment as usual at high levels of conflict, and the opposite at low levels of conflict. This is not the case for conflict with father. For adolescent report the posterior distribution of the regression coefficient for a moderator effect has a mean of approximately 0, implying no moderation. For father report, the moderator model implies that parent-adolescent conflict is associated with worse or better outcomes in treatment as usual only, but that outcome in ABFT does not vary over father-reported conflict.

TABLE 3. Parameter estimates from moderator models

	Conflict report and model parameter					
	Mean	SD	Median	66% HDI	90% HDI	ESS
Adolescent report of conflict with mother						
Intercept	0.09	0.09	0.09	0.00 ; 0.17	-0.05 ; 0.24	11801
Variance of random intercepts	0.36	0.13	0.37	0.28 ; 0.50	0.14 ; 0.56	1764
Variance of errors	0.53	0.08	0.53	0.45 ; 0.59	0.41 ; 0.65	2382
Regression coefficients						
Time	-0.53	0.15	-0.53	-0.65 ; -0.37	-0.78 ; -0.29	10094
Treatment	0.01	0.18	0.01	-0.16 ; 0.18	-0.29 ; 0.30	10608
Parent-adolescent conflict	0.27	0.29	0.27	-0.01 ; 0.55	-0.21 ; 0.76	7372
Treatment x time	0.07	0.11	0.07	-0.04 ; 0.17	-0.12 ; 0.25	9108
Conflict x time	0.15	0.19	0.15	-0.03 ; 0.31	-0.16 ; 0.47	7425
Treatment x conflict x time	-0.69	0.34	-0.70	-1.01 ; -0.38	-1.25 ; -0.15	5919
Adolescent report of conflict with father						
Intercept	0.09	0.09	0.09	0.00 ; 0.18	-0.07 ; 0.24	12959
Variance of random intercepts	0.36	0.13	0.38	0.27 ; 0.51	0.14 ; 0.58	2059
Variance of errors	0.58	0.08	0.57	0.49 ; 0.64	0.45 ; 0.69	2853
Regression coefficients						
Time	-0.49	0.16	-0.48	-0.64 ; -0.34	-0.75 ; -0.23	11610
Treatment	0.00	0.19	0.00	-0.19 ; 0.16	-0.30 ; 0.31	11630
Parent-adolescent conflict	0.20	0.31	0.20	-0.07 ; 0.51	-0.29 ; 0.71	11097
Treatment x time	0.04	0.1	0.04	-0.06 ; 0.13	-0.13 ; 0.21	10099
Conflict x time	0.13	0.22	0.13	-0.07 ; 0.34	-0.24 ; 0.47	5198
Treatment x conflict x time	0.01	0.40	0.00	-0.38 ; 0.36	-0.60 ; 0.70	4474
Mothers report of conflict						
Intercept	0.09	0.09	0.09	0.00 ; 0.17	-0.05 ; 0.25	12613
Variance of random intercepts	0.37	0.12	0.39	0.29 ; 0.50	0.18 ; 0.58	2008
Variance of errors	0.54	0.08	0.54	0.46 ; 0.60	0.41 ; 0.66	2488
Regression coefficients						
Time	-0.55	0.15	-0.54	-0.69 ; -0.4	-0.80 ; -0.30	10341
Treatment	-0.03	0.18	-0.03	-0.21 ; 0.13	-0.33 ; 0.26	11666
Parent-adolescent conflict	0.19	0.30	0.20	-0.07 ; 0.51	-0.29 ; 0.70	8534
Treatment x time	-0.08	0.11	-0.08	-0.18 ; 0.02	-0.26 ; 0.09	9297
Conflict x time	-0.02	0.19	-0.02	-0.19 ; 0.16	-0.33 ; 0.28	6471
Treatment x conflict x time	-0.67	0.34	-0.68	-1.01 ; -0.38	-1.22 ; -0.11	6593
Fathers report of conflict						
Intercept	0.09	0.09	0.09	0 ; 0.17	-0.05 ; 0.24	9540
Variance of random intercepts	0.37	0.12	0.38	0.29 ; 0.5	0.17 ; 0.57	1651
Variance of errors	0.51	0.08	0.50	0.43 ; 0.58	0.38 ; 0.64	1740
Regression coefficients						
Time	-0.54	0.16	-0.54	-0.68 ; -0.38	-0.79 ; -0.27	5165
Treatment	-0.01	0.18	-0.01	-0.18 ; 0.16	-0.32 ; 0.26	10840
Parent-adolescent conflict	0.30	0.30	0.30	0.01 ; 0.59	-0.19 ; 0.81	5729
Treatment x time	-0.03	0.11	-0.03	-0.13 ; 0.08	-0.21 ; 0.16	6466
Conflict x time	0.41	0.24	0.41	0.18 ; 0.61	0.03 ; 0.81	2780
Treatment x conflict x time	-0.86	0.44	-0.87	-1.28 ; -0.46	-1.60 ; -0.17	2701

Note. Mean = Posterior mean, SD = Posterior standard deviation, Median = Posterior median, 66% and 90% HDI = 66% and 90% Highest Density Intervals, ESS = Effective Sample Size, estimates the number of independent draws from the posterior distribution

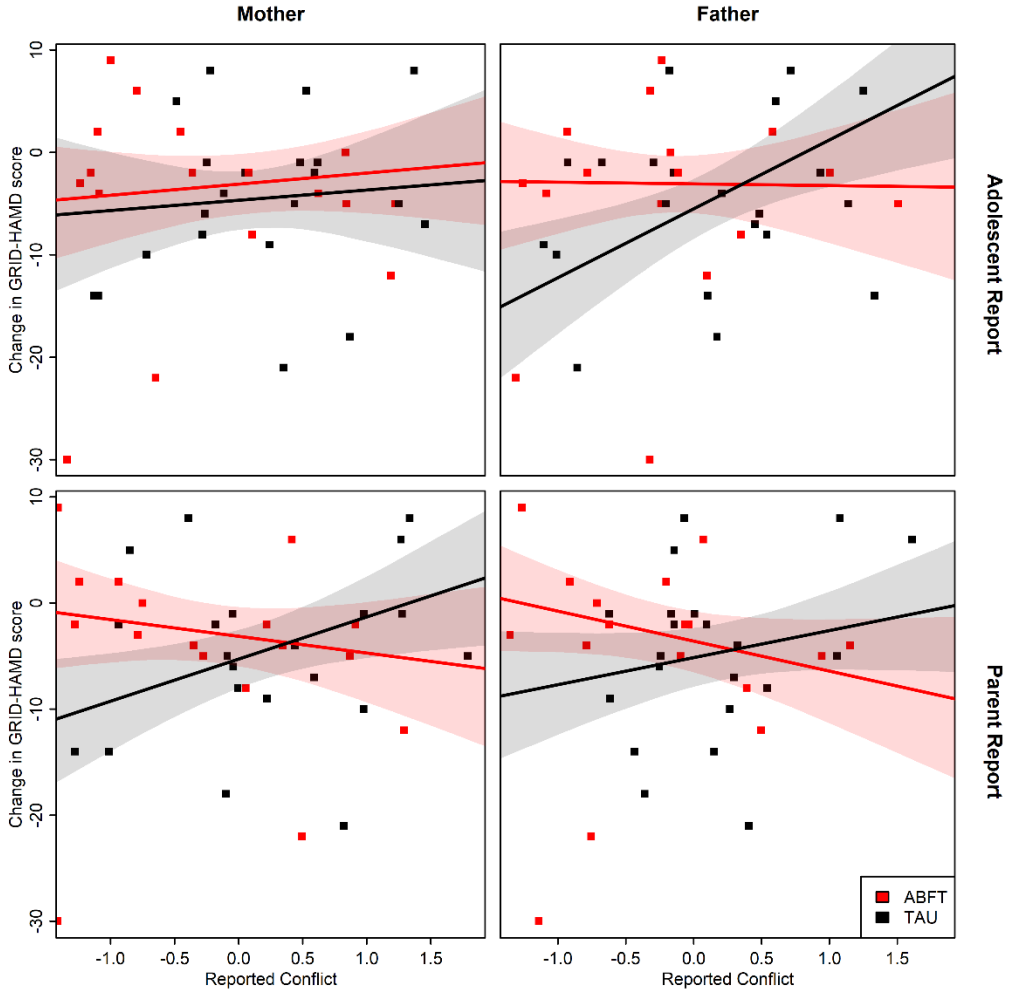

FIGURE 2. Model predictions across the range of conflict for different informants

TABLE 4. Correlation coefficients for latent conflict variables (Posterior means and 90% CI)

	Adolescent on father	Adolescent on mother	Father on adolescent
Adolescent on mother	0.20 (-0.06 ; 0.46)		
Father on adolescent	0.59 (0.39 ; 0.79)	0.33 (0.04 ; 0.62)	
Mother on adolescent	0.03 (-0.21 ; 0.27)	0.49 (0.28 ; 0.73)	0.50 (0.26 ; 0.75)

TABLE 5. Model comparison with leave-one-out cross-validation

Reporter and models compared	Difference	SE
Adolescent report of conflict with mother		
Time	0	0
Moderator	-1.86	1.36
Treatment	-1.87	0.14
Non-specific predictor	-3.91	0.71
Adolescent report of conflict with father		
Time	0	0
Treatment	-1.87	0.14
Non-specific predictor	-3.74	0.31
Moderator	-5.57	0.40
Mother report of conflict		
Time	0	0
Treatment	-1.87	0.14
Moderator	-3.02	1.32
Non-specific predictor	-4.47	0.30
Father report of conflict		
Time	0	0
Treatment	-1.87	0.14
Moderator	-2.34	1.86
Non-specific predictor	-4.54	0.77

Note. Difference = Difference in expected log posterior density to the best-fitting model of those compared; SE = Standard error of the difference

Using cross-validation to evaluate expected out-of-sample model fit

Table 5 shows the differences in ELPD (expected log posterior density, obtained by LOO-CV) between the four models that were compared. It should be noted that the standard errors of these differences are known to be optimistic, especially in small samples, and a difference of four standard errors or more has been recommended for selection of one model over another (42, 46).

Cross-validation clearly shows that the model "Time" has a better expected out-of-sample fit than "Treatment", with a difference in ELPD larger than ten times the standard error. The model "Time" also fits better than the model "Non-specific predictor" across all four informants, with differences in ELPD of more than five standard errors. The picture is less clear for the comparison of the "Moderator" model to "Time". For adolescent report of conflict with father "Time" is clearly better, with a difference larger than ten times the standard error. For father-report of conflict, and for adolescent and mother report of conflict with mother, the differences are too small relative to their standard errors to support selecting either model over the other.

Discussion

Our findings have considerable uncertainty, and the predicted differences in treatment outcome related to parent-adolescent conflict are clinically meaningful (47) only in the higher and lower quantiles of the distribution of parent-adolescent conflict. This is not surprising, given the overall small average treatment effect in the trial (22). For mother-adolescent conflict, there is some evidence of a moderator effect. The posterior distributions of the regression coefficients indicate that a moderator effect is more probable than equal effects of treatment across the range of mother-adolescent conflict, regardless of adolescent or parent report. Cross-validation suggests that either the model with a weak effect of time or the moderator model will give the best out-of-sample predictions. Adolescent report of conflict with father does not appear to be associated with treatment outcome, and cross-validation here clearly supports the model with an effect of time alone. For father report of conflict, the fitted moderator model implies an association with outcome restricted to treatment as usual, with the same results of cross-validation as for the models for mother-adolescent conflict.

Earlier studies have found parent-adolescent conflict, in particular with mother, to negatively impact outcomes of various treatments for adolescent depression (10-12). Our findings are similar for treatment as usual in two Norwegian CAMHS, giving further evidence for parent-adolescent conflict as a negative predictor of outcome in treatment of adolescent depression, although in our case not for adolescent report of conflict with father. Further, we found some evidence that in a family-based treatment, the reverse association may hold, in particular for mother-adolescent conflict. This is also in line with the

findings from other studies (13-15), although findings from a secondary analysis of the largest trial conducted by the ABFT treatment developers did not show this pattern (20). That study found adolescent report of family conflict and cohesion to be a non-specific predictor of reduction in suicidal ideation, but no evidence of moderation. However, those findings may not be directly comparable to the ones presented here, as their measure of general perceptions of family climate arguably assesses a different construct than the CBQ, which assesses the perception of distressing conflict in a specific dyadic relationship (33).

The pattern of moderation implied by the fitted model is worth noting, as the predicted outcomes of the two treatments compared appear to show roughly opposite associations with mother-adolescent conflict. This is an example of a moderator effect one would not necessarily suspect by looking at the residuals of a simpler model, as the error variances would not differ substantially between treatment groups even with a stronger moderation effect.

Although this is speculative, such a pattern of moderation could perhaps explain the unexpected findings of the two latest trials of ABFT (19, 22), where ABFT did not perform better than active comparisons, even though previous findings have been promising (17). In developing and early testing of ABFT, the patient group has been predominantly composed of youth from disadvantaged neighbourhoods, with many families suffering from financial strain (48). Financial strain has been shown to increase the frequency and severity of parent-adolescent conflict (e.g. 49), and was found to predict higher treatment benefit of ABFT and family-enhanced non-directive supportive therapy (20). The degree of variation in and level of parent-adolescent conflict among patients participating in early development of ABFT has not been reported, as far as we know. It is therefore possible that the effectiveness of ABFT is more dependent on the presence of parent-adolescent conflict and other relationship difficulties than previously thought. The findings presented in the present paper are too uncertain to permit a definitive conclusion, but indicate that this issue would bear further investigation.

Limitations and strengths

This study has multiple limitations that must be taken into account. Firstly, the trial did not meet its planned sample size, and the resulting sample is small. Further, the proportion of missing outcome data was considerable. This lack of data is well reflected in the uncertainty of the reported results, which is an advantage of Bayesian data analysis, where both the small sample and the missing data are taken into account in the posterior distribution. Secondly, the number of male adolescents in the sample is very low, and the results cannot be generalised to the male adolescent population.

A third limitation is that the adherence and competence of the ABFT therapists were not systematically assessed. Without systematic ratings of adherence and competence, we cannot conclude with certainty that the treatment provided in the ABFT treatment arm was according to the treatment manual (16). The therapists had training and some supervision from an experienced and certified ABFT therapist. All had completed one case under supervision previous to treating randomised cases, in addition to their previous general clinical experience. The therapists nevertheless lacked extensive experience with the ABFT treatment model, which is both technically and personally demanding (16), and had less supervision than in other ABFT clinical trials (19, 48, 50). The trial as such represents a reasonably realistic test of the efficiency of ABFT when implemented with the level of effort that can be expected within the regular operations and financing of a Norwegian CAMHS. This gives the study good ecological validity, further increased by TAU being the literal treatment as usual provided by the CAMHS. Other strengths of the study are reporting on a moderator analysis with a clear theoretical justification and employing modern estimation and modelling techniques.

Clinical significance

The hypothesis that the treatment effect of ABFT relative to treatment as usual would be moderated by parent-adolescent conflict received some support. However, the results are too uncertain to be appropriate for informing clinical practice. Further studies should investigate whether parent-adolescent conflict and other strains in the parent-adolescent relationship moderate the effectiveness of ABFT relative to other treatments. Given recent findings that suggest the average effect of ABFT to differ little from treatment models that may be less demanding to implement (19), it would be important to determine whether subgroups of depressed adolescents could benefit relatively more from ABFT, in particular subgroups known to be doing poorly in other treatments.

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Conflicts of interest
The authors declare that they have no conflict of interest.

Ethics approval
All procedures performed were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments. The study protocol, participant information letters and consent forms were reviewed and approved by the Regional Committee for Medical and Health Research Ethics for Eastern Norway (REK Øst).

Consent to participate
Informed consent was obtained from all individual participants included in the study, or their legal guardians, in which case assent to be included in the study was obtained from the underage participant.

Code availability
Stan and R code from the analysis, as well as the fitted models (including posterior samples) and results of LOO-CV is available at doi:10.17605/OSF.IO/KPJC6.

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