

Algorithm-based modular psychotherapy vs. cognitive-behavioral therapy for patients with depression, psychiatric comorbidities and early trauma: a proof-of-concept randomized controlled trial

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Effect sizes of psychotherapies currently stagnate at a low-to-moderate level. Personalizing psychotherapy by algorithm-based modular procedures promises improved outcomes, greater flexibility, and a better fit between research and practice. However, evidence for the feasibility and efficacy of modular-based psychotherapy, using a personalized treatment algorithm, is lacking. This proof-of-concept randomized controlled trial was conducted in 70 adult outpatients with a primary DSM-5 diagnosis of major depressive disorder, a score higher than 18 on the 24-item Hamilton Rating Scale for Depression (HRSD-24), at least one comorbid psychiatric diagnosis according to the Structured Clinical Interview for DSM-5 (SCID-5), a history of at least “moderate to severe” childhood maltreatment on at least one domain of the Childhood Trauma Questionnaire (CTQ), and exceeding the cut-off value on at least one of three measures of early trauma-related transdiagnostic mechanisms: the Rejection Sensitivity Questionnaire (RSQ), the Interpersonal Reactivity Index (IRI), and the Difficulties in Emotion Regulation Scale-16 (DERS-16). Patients were randomized to 20 sessions of either standard cognitive-behavioral therapy alone (CBT) or CBT plus transdiagnostic modules according to a mechanism-based treatment algorithm (MoBa), over 16 weeks. We aimed to assess the feasibility of MoBa, and to compare MoBa vs. CBT with respect to participants’ and therapists’ overall satisfaction and ratings of therapeutic alliance (using the Working Alliance Inventory - Short Revised, WAI-SR), efficacy, impact on early trauma-related transdiagnostic mechanisms, and safety. The primary outcome for efficacy was the HRSD-24 score at post-treatment. Secondary outcomes included, among others, the rate of response (defined as a reduction of the HRSD-24 score by at least 50% from baseline and a score <16 at post-treatment), the rate of remission (defined as a HRSD-24 score ≤8 at post-treatment), and improvements in early trauma-related mechanisms of social threat response, hyperarousal, and social processes/empathy. We found no difficulties in the selection of the transdiagnostic modules in the individual patients, applying the above-mentioned cut-offs, and in the implementation of MoBa. Both participants and therapists reported higher overall satisfaction and had higher WAI-SR ratings with MoBa than CBT. Both approaches led to major reductions of depressive symptoms at post-treatment, with a non-significant superiority of MoBa over CBT. Patients randomized to MoBa were nearly three times as likely to experience remission at the end of therapy (29.4% vs. 11.4%; odds ratio, OR = 3.2, 95% CI: 0.9-11.6). Among mechanism-based outcomes, MoBa patients showed a significantly higher post-treatment effect on social processes/empathy ($p < 0.05$) compared to CBT patients, who presented an exacerbation on this domain at post-treatment. Substantially less adverse events were reported for MoBa compared to CBT. These results suggest the feasibility and acceptability of an algorithm-based modular psychotherapy complementing CBT in depressed patients with psychiatric comorbidities and early trauma. While initial evidence of efficacy was observed, potential clinical advantages and interindividual heterogeneity in treatment outcomes will have to be investigated in fully powered confirmation trials.

Key words: Depression, early trauma, algorithm-based modular psychotherapy, mechanism-based treatment, cognitive-behavioral therapy, transdiagnostic treatment modules, trauma-related mechanisms, social processes, empathy

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In more than seven decades of research, psychotherapy has come a long way in proving its effects in treating mental health problems. Much research was stimulated by the development of disorder-specific approaches, particularly in the field of cognitive-behavioral therapy (CBT). However, this continuing evolution has not been paralleled by improved treatment outcomes.

Most evidence-based psychotherapy protocols are based on single-disorder specific manuals, disregarding common psychiatric comorbidities, transdiagnostic vulnerability factors such as early trauma, and the high phenomenological heterogeneity among patients. This mismatch between available disorder-specific protocols and individual patient characteristics diminishes treatment effects and may be one reason for the limited application of evidence-based psychotherapies in clinical practice.

Effect sizes of psychotherapies in general are currently stagnating at a low-to-moderate level. In the field of depression, a minimum of 50% of patients do not respond, with approximately two-thirds not achieving remission with first-line treatment¹, even when the procedure is in accordance with treatment guidelines^{2,3}.

Fueled by growing criticism that disorder-specific manuals fail to address an individual’s complexity of transdiagnostic dysfunctional mechanisms and processes, research paradigms are currently shifting toward personalization of psychotherapy⁴⁻⁶. By taking differential treatment effects and interindividual differences into account, personalized psychotherapy could yield greater flexibility, improved outcomes, and a better fit between research and practice.

Within this movement, several distinct approaches have emerged recently. One such pathway to achieve personalization is modular therapy⁷⁻¹⁰. In contrast to conventional treatment protocols, modular approaches provide clinicians with an evidence-based toolbox, allowing to integrate treatment modules systematically, as independent but combinable sets of functional units. By tailoring module selection and application to the specific characteristics and needs of each patient, modular therapy promises higher acceptance by patients and therapists as well as better treatment outcomes¹¹.

Modularity as a fundamental treatment principle was estab-

lished two decades ago and has been primarily researched in children and adolescents^{7,12}. In adults, several feasibility trials with modular interventions have recently been conducted for a variety of mental health problems, with encouraging results¹³⁻¹⁷. However, up to now, there has been little information on the decision criteria used to select interventions. Notably, programs have not applied algorithms to choose the modules according to patients' characteristics in order to systematically personalize the treatment procedure.

Only one contemporary study provides initial evidence for the feasibility of statistical decision-making algorithms to guide mental health care¹⁸. However, the efficacy cannot be clearly assessed, as only pre-post results from an uncontrolled open trial in community college students are available to date¹⁹.

The present study is the first to investigate algorithm-based modular psychotherapy for adult patients in an observer-blinded, randomized controlled trial. To represent a difficult-to-treat sample regularly seen in clinical practice, patients with a DSM-5 diagnosis of major depressive disorder, a score higher than 18 on the 24-item Hamilton Rating Scale for Depression (HRSD-24)²⁰, at least one psychiatric comorbidity, a history of at least "moderate to severe" childhood maltreatment, and disturbed early trauma-related transdiagnostic mechanisms according to Research Domain Criteria (RDoC)²¹, were included.

The aim of the study was to evaluate the feasibility and acceptability, and to provide preliminary evidence for the efficacy of modular-based psychotherapy (MoBa) using a personalized treatment algorithm. This algorithm was derived from empirical evidence on the shared mechanisms underlying mental disorders after early trauma. These include overactivation of the fear/threat system, and dysfunctions of the arousal/affect regulation and social cognition systems²²⁻²⁴.

The primary outcome for efficacy was the HRSD-24 score at the end of treatment. Secondary outcomes included, among others, the response and remission rate, and improvements in the early trauma-related mechanisms of social threat response, hyperarousal, and social processes/empathy.

METHODS

Study design and participants

In this parallel-arm, observer-blinded, randomized controlled trial (RCT), 70 early-traumatized outpatients with depression and psychiatric comorbidities were recruited at two German university psychiatric centers.

Eligible patients were 18-65 years old; had a primary DSM-5 diagnosis of major depressive disorder ascertained by the Structured Clinical Interview for DSM-5 (SCID-5)²⁵; had a score higher than 18 on the HRSD-24²⁰; had at least one comorbid psychiatric diagnosis according to the SCID-5; had a history of at least "moderate to severe" childhood maltreatment on at least one domain of the Childhood Trauma Questionnaire (CTQ)²⁶ (i.e., emotional neglect, emotional abuse, physical neglect, physical abuse, or sexual abuse); and exceeded the cut-off value on at least one of

three measures of early trauma-related transdiagnostic mechanisms^{23,27}, i.e., a score ≥ 9.88 on the Rejection Sensitivity Questionnaire (RSQ)²⁸; a score < 45 on the Interpersonal Reactivity Index (IRI)²⁹, or a score ≥ 55.73 on the Difficulties in Emotion Regulation Scale-16 (DERS-16)³⁰.

Exclusion criteria were: an acute risk of suicide; another psychiatric disorder as the primary diagnosis; fulfilling diagnostic criteria for schizophrenia, bipolar I disorder, neurocognitive disorder, or substance use disorder during the last 6 months; a diagnosis of antisocial personality disorder or more than three traits of borderline personality disorder according to the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5 PD)³¹; severe cognitive impairment; a serious medical condition (interfering with participation in therapy sessions); other ongoing psychotherapy or psychotropic medication, except antidepressant and/or sleep-inducing treatment, if stable for at least 3 weeks (4 weeks for fluoxetine). The selective use of a benzodiazepine as rescue medication on-demand for a maximum of 2 weeks was permitted, while the continuous intake of a benzodiazepine was not allowed³².

The study protocol was approved by the independent Ethics Committees of the University of Freiburg (reference no. 414/20) and the University of Heidelberg (reference no. S-762/2020). The trial was preregistered at the German Clinical Trials Register (registration no. DRKS00022093). All participants provided written informed consent.

Randomization, masking and monitoring

Randomization was performed, stratified by site, in blocks of variable length in a ratio of 1:1. The block lengths were documented separately and not disclosed to the sites. All clinical interviews and outcome assessments were conducted by raters who were blinded to the treatment arm allocation.

The raters were centrally trained and certified in the assessment of clinician-rated outcomes, and inter-rater reliability was ensured as part of the training process. The sites implemented procedures to maintain rater blinding to treatment assignment by informing and reminding patients, at each visit, not to mention their treatment condition or related content to the raters. In addition, the raters and the study therapists were placed at different physical locations. Therapists refrained from any conversation about any aspects of individual treatments with the raters. On-site data monitoring was regularly conducted by clinical monitors from the Clinical Trials Unit Freiburg.

Interventions

The interventions included 20 manual-based individual sessions of CBT or MoBa over 16 weeks (twice weekly in weeks 1-4, once per week in weeks 5-16).

The CBT condition followed the German standard CBT manual for depression³³, including the following elements: building a therapeutic alliance, psychoeducation, behavior activation, cognitive re-

structuring, and strategies for maintenance and relapse prevention.

The MoBa condition included CBT as described above, complemented by at least one of three selected modules, which addressed disturbed mechanisms associated with early interpersonal traumatization.

Module 1 addressed the negative valence system (according to RDoC²¹) and the social threat response system, with the goal to reduce avoidance behavior. It used elements of the cognitive behavioral analysis system of psychotherapy (CBASP)^{34,35}, a method tailored for the treatment of early-onset chronically depressed patients, usually with a trauma history. The CBASP elements included in the module were the “significant other history” with a derived transference hypothesis, the “interpersonal discrimination exercise”, and the therapist’s “contingent personal reactivity” (see also supplementary information). The questionnaire assessing the domains covered by this module was the RSQ²⁸.

Module 2 addressed the system for social processes (according to RDoC²¹), with the goal of enhancing perception and understanding of self and others, empathy and social communication. It used strategies of mentalization-based therapy (MBT)³⁶. This included modelling and teaching mentalization, so that the patient could learn to “read” others’ behavior and was thereby reconnected to his/her social environment, fostering his/her social competence (see also supplementary information). The questionnaire assessing the domains covered by this module was the IRI²⁹.

Module 3 addressed the arousal system (according to RDoC²¹), with the goal of reducing hyperarousal. It used the emotion awareness and regulation techniques of mindfulness-based cognitive therapy (MBCT)³⁷. This included mindfulness exercises focusing on: observing non-judgmentally internal and external stimuli; shifting attention away from trauma-related inner “movies”; and monitoring skills to overcome hyperarousal or being run over by one’s emotions (see also supplementary information). The questionnaire assessing the domains covered by this module was the DERS-16³⁰.

The study therapists, who were clinical psychologists with a CBT background, received a formal training in both manualized interventions by experts of the respective fields. Adherence to the manuals was assured by continuous supervision. All therapy sessions were video-recorded, and randomly selected sequences were watched by the supervisors. In addition, adherence was checked by asking therapists to fill out a Therapeutic Element Checklist (TEC) (see supplementary information) immediately after each session. Supervisors reviewed the TECs regularly.

Outcomes and assessments

We investigated the feasibility of the selection of the therapeutic modules in the individual patients – applying the above-mentioned cut-off values for measures of early trauma-related transdiagnostic mechanisms – and of the implementation of MoBa. Participants’ and therapists’ overall satisfaction with MoBa and CBT was assessed by the TEC after each session. The therapeutic alliance was evaluated by participants and therapists using the

Working Alliance Inventory - Short Revised (WAI-SR)³⁸ at the end of treatment. The WAI-SR assesses three key aspects of the therapeutic alliance: agreement on tasks of therapy, agreements on goals of therapy, and development of an affective bond.

The primary efficacy outcome was defined *a priori* as the HRSD-24²⁰ score at the end of treatment measured by blind, independent raters. Secondary outcomes included the rate of response (defined as a reduction of the HRSD-24 score by at least 50% from baseline and a score <16 at post-treatment), and the rate of remission (defined as a HRSD-24 score ≤8 at post-treatment).

Further secondary outcomes comprised: a) self-rated depressive and anxiety symptoms, as assessed by the Beck Depression Inventory-II (BDI-II)³⁹ and the Beck Anxiety Inventory (BAI)⁴⁰; b) improvements in the early trauma-related mechanisms of social threat response, hyperarousal, and social processes/empathy, as assessed by the RSQ²⁸, the DERS-16³⁰, and the IRI²⁹, respectively; c) improvements in clinician-rated social and occupational functioning, as assessed by the Social and Occupational Functioning Assessment Scale (SOFAS)⁴¹, and in self-rated quality of life, as assessed by the World Health Organization Quality of Life - Brief Version (WHOQOL-BREF)⁴².

We also assessed the deterioration rate, in both treatment groups, using the reliable change index based on the variance and reliability of the HRSD-24 score at baseline and post-treatment.

Adverse events and serious adverse events were recorded for the entire treatment duration, using a well-established checklist⁴³. Adverse events were defined as any unfavorable and unintended sign, symptom or disease, whether or not considered to be related to the treatment (this included worsening of symptoms, occurrence of new symptoms, occurrence of passive suicidal thoughts, active suicidal intentions or plans, problems in the patient-therapist relationship, private problems, occupational problems, or other medical conditions). Serious adverse events were defined as any medical event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity (this included any medical condition that might require medical or surgical intervention to prevent one of the above outcomes, including suicide attempts).

Statistical analyses

Due to the exploratory nature of the trial and the lack of comparable studies, no formal sample size calculation was possible³². Following Billingham et al⁴⁴, a sample size of 30 patients per group was regarded as reasonable, resulting in a total of 60 patients. Non-compliance and/or dropout of patients after randomization was assumed to be at most 14%. Therefore, 70 patients were randomized, split in the two treatment groups for each of the two participating centers.

The primary efficacy analysis was performed according to the intention-to-treat principle and was based on the full analysis set. This included all randomized patients, who were analyzed as belonging to their randomized arm, regardless of whether they re-

fused therapy, or whether other protocol deviations were known. The effects of CBT and MoBa with respect to the HRSD-24 post-treatment (primary endpoint) were estimated within a linear regression model and the two-sided 95% confidence interval (CI). The model included treatment and study center as independent variables, as well as baseline HRSD-24 score.

Secondary endpoints were analyzed descriptively in a similar fashion, using regression models as appropriate for the respective type of data. Treatment effects were calculated with corresponding two-sided 95% CIs.

The primary and secondary endpoints were also evaluated in linear regression models as described above, but additionally adjusting for the depression type (episodic depressive disorder vs. persistent depressive disorder or dysthymic syndrome with superimposed major depressive episodes).

RESULTS

A total of 119 patients were screened for eligibility at both centers from December 2019 to March 2022, of whom 70 were included and randomized to MoBa or CBT. One patient in the MoBa group discontinued the study due to relocation. Four patients (three in MoBa, one in CBT) dropped out after less than 17 sessions. All patients were included in the intention-to-treat analysis (see Figure 1).

Sample characteristics

Demographic, historical and clinical baseline characteristics of the participants in the intention-to-treat sample are shown in Table 1. The mean age was 38.9 ± 13.2 years in the MoBa group and

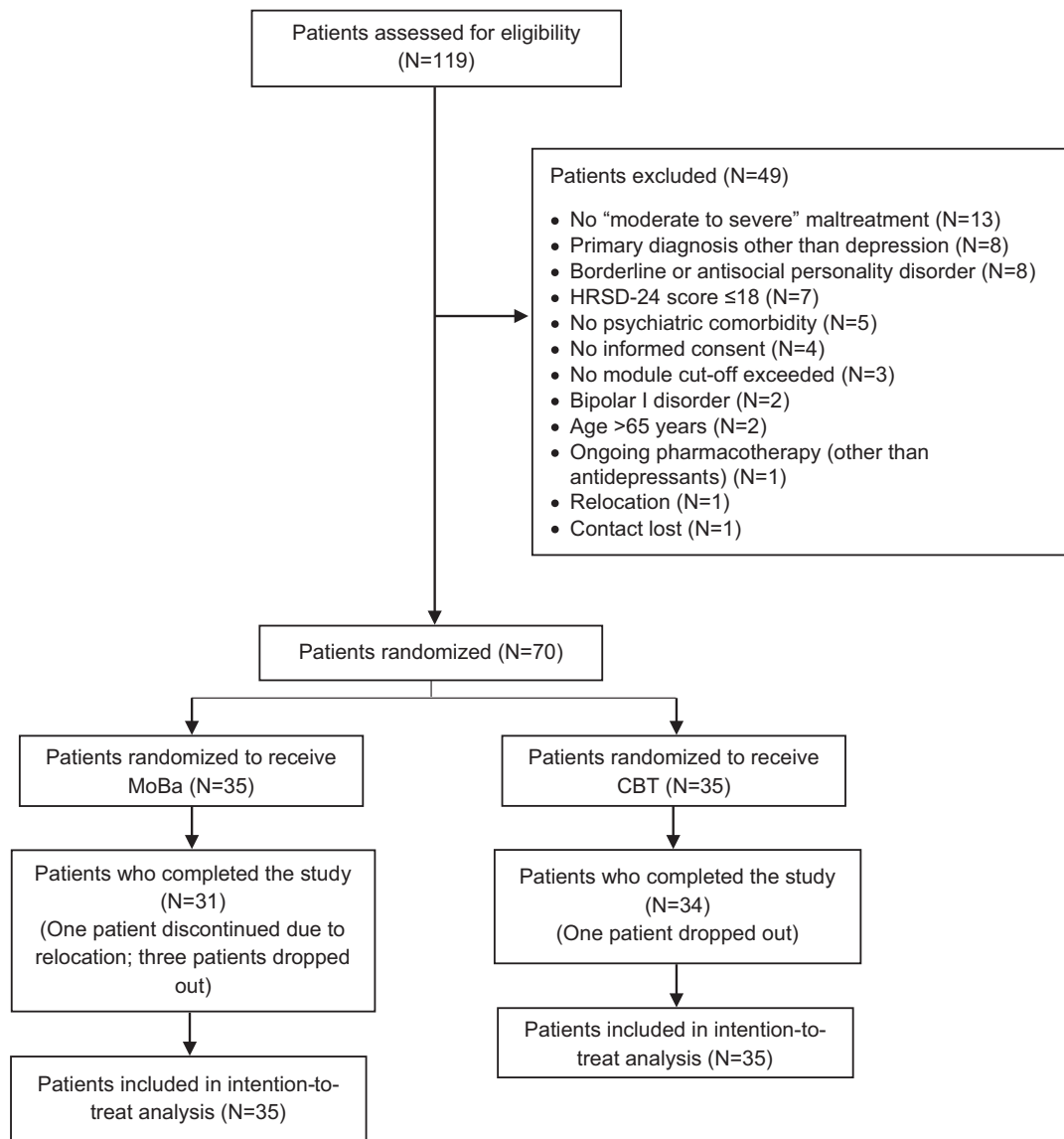


Figure 1 Study flow chart. MoBa – algorithm-based modular psychotherapy, CBT – standard cognitive-behavioral therapy, HRSD-24 – 24-item Hamilton Rating Scale for Depression.

Table 1 Demographic, historical and clinical baseline characteristics of participants in the study

	MoBa (N=35)	CBT (N=35)
Age (years), mean±SD	38.9±13.2	44.4±15.3
Gender, N (%)		
Female	25 (71.4)	24 (68.6)
Male	10 (28.6)	10 (28.6)
Non-binary	0	1 (2.9)
Marital status, N (%)		
Single	15 (42.9)	19 (55.9)
Married/registered partnership	7 (20.0)	5 (14.7)
Permanent partnership	10 (28.6)	1 (2.9)
Divorced/separated	3 (8.6)	9 (26.5)
Widowed	0	0
Educational level, N (%)		
Low (less than 9 years)	2 (5.7)	2 (5.7)
Medium (10-11 years)	7 (20.0)	11 (31.4)
High (12+ years)	26 (74.3)	22 (62.9)
Employment, N (%)		
Full-time	5 (15.2)	4 (11.8)
Part-time	7 (21.2)	9 (26.5)
Marginally/irregularly employed	8 (24.2)	3 (8.8)
In training	2 (6.1)	2 (5.9)
Not employed	11 (33.3)	16 (47.1)
Depression type, N (%)		
Episodic depressive disorder	11 (31.4)	20 (57.1)
Persistent depressive disorder	12 (34.3)	7 (20.0)
Dysthymic syndrome with superimposed major depressive episodes	12 (34.3)	8 (22.9)
Age at first depressive episode (years), mean±SD	20.1±11.4	20.0±9.3
Family history of mental disorder, N (%)	27 (77.1)	23 (65.7)
Comorbid psychiatric diagnoses (number), mean±SD	1.9±0.9	1.9±1.1
Childhood maltreatment in individual CTQ domains, N (%)		
Emotional neglect	32 (91.4)	29 (82.9)
Emotional abuse	25 (71.4)	27 (77.1)
Physical neglect	14 (40.0)	11 (31.4)
Physical abuse	10 (28.6)	10 (28.6)
Sexual abuse	11 (31.4)	7 (20.6)
CTQ domains on which maltreatment was reported, N (%)		
One	8 (22.9)	10 (28.6)
Two	8 (22.9)	12 (34.3)
Three	10 (28.6)	6 (17.1)

Table 1 Demographic, historical and clinical baseline characteristics of participants in the study (*continued*)

	MoBa (N=35)	CBT (N=35)
Four	7 (20.0)	3 (8.6)
Five	2 (5.7)	4 (11.4)
CTQ domains on which maltreatment was reported, mean±SD	2.6±1.2	2.4±1.3
Previous suicide attempts, N (%)		
None	23 (65.7)	29 (82.9)
One	9 (25.7)	2 (5.7)
At least two	3 (8.6)	4 (11.4)
Previous inpatient psychiatric treatment, N (%)		
Yes	16 (45.7)	11 (31.4)
No	19 (54.3)	24 (68.6)
Current HRSD-24 score, mean±SD	26.3±4.7	27.6±7.3
Current physical comorbidities, N (%)	20 (57.1)	15 (42.9)
Currently receiving psychopharmacological treatment, N (%)	21 (60.0)	25 (71.4)

MoBa – algorithm-based modular psychotherapy, CBT – standard cognitive-behavioral therapy, HRSD-24 – 24-item Hamilton Rating Scale for Depression, CTQ – Childhood Trauma Questionnaire

44.4±15.3 years in the CBT sample. The proportion of females was, respectively, 71.4% and 68.6%. Most patients were single (42.9% and 55.9%) and not employed (33.3% and 47.1%) in both groups.

Patients in the MoBa group had more frequently a diagnosis of persistent depressive disorder (34.3% vs. 20.0%) or dysthymic syndrome with superimposed major depressive episodes (34.3% vs. 22.9%). The current mean HRSD-24 score was 26.3±4.7 in MoBa and 27.6±7.3 in CBT patients. The mean duration of the current depressive condition was 204 days in MoBa and 142 days in CBT patients. Patients in the MoBa arm reported twice as many past suicide attempts prior to treatment (34.3% vs. 17.1%) and were more likely to present current physical comorbidities (57.1% vs. 42.9%).

The mean number of comorbid psychiatric diagnoses was 1.9 in both groups (range: 1-5). Anxiety disorders were the most frequent comorbid diagnoses (27.1% of patients were diagnosed with generalized anxiety disorder, 22.9% with social anxiety disorder, 14.3% with panic disorder, 14.3% with specific phobia, and 7.1% with agoraphobia). Furthermore, 25.7% of patients received a comorbid diagnosis of personality disorder (20.0% avoidant, 2.9% dependent, 1.4% narcissistic, and 1.4% obsessive-compulsive); 21.4% had comorbid post-traumatic stress disorder; 15.7% attention-deficit/hyperactivity disorder (ADHD); 11.4% obsessive-compulsive or related disorders; 7.1% sleep-wake disorders; 5.8% feeding or eating disorders; 4.3% premenstrual dysphoric disorder; and 4.3% unspecified somatic symptom and related disorders.

Childhood maltreatment (at least “moderate to severe”) was reported in a mean number of CTQ domains of 2.6±1.2 for the MoBa and 2.4±1.3 for the CBT group. Overall, 87.1% of patients experienced emotional neglect (35.7% “moderate to severe”, 51.4%

“severe to extreme”); 74.3% emotional abuse (22.9% “moderate to severe”, 51.4% “severe to extreme”); 35.7% physical neglect (15.7% “moderate to severe”, 20.0% “severe to extreme”); 28.6% physical abuse (10.0% “moderate to severe”, 18.6% “severe to extreme”); and 26.1% sexual abuse (13.0% “moderate to severe”, 13.0% “severe to extreme”).

The proportion of patients currently receiving psychopharmacological treatment was 60.0% in the MoBa and 71.4% in the CBT group. Overall, 65.7% of patients were receiving medication. Of these, 17.1% reported the stable use of selective serotonin reuptake inhibitors, 12.9% of non-selective monoamine reuptake inhibitors, 42.9% of other antidepressants. The proportion of patients with a history of inpatient psychiatric treatment was 45.7% in the MoBa and 31.4% in the CBT sample.

Module allocation and treatment implementation

In the MoBa group, treatment modules were selected in the individual patients according to a systematic algorithm applying the above-mentioned cut-off values for measures of early trauma-related transdiagnostic mechanisms. Among patients randomized to this group, 17.1% received only the Module 1; 11.4% only the Module 2; 14.3% the Modules 1 and 2; 31.4% the Modules 1 and 3; 2.9% the Modules 2 and 3; and 22.9% the Modules 1, 2 and 3. No patient

received only the Module 3 (see Figure 2).

Overall, patients received a mean of 17.3±4.0 therapy sessions. In the MoBa group, the mean time in a session applying CBT elements was 43.2%. If CBASP and/or mentalization and/or mindfulness elements were part of the modular intervention, the mean time spent on each of these elements was, respectively, 50.5%, 45.9%, and 33.9%.

Feasibility and acceptability

We found no difficulties in the selection of the therapeutic modules in the individual patients – by applying the above-mentioned cut-off values for measures of early trauma-related transdiagnostic mechanisms – and in the implementation of MoBa.

Therapists recorded high or very high satisfaction more frequently after a modular therapy session than after a CBT session (92.8% vs. 82.9%). The same applied to patients (82.9% vs. 74.3%). Difficulties in the patient-therapist relationship were reported by 5.7% of patients in the MoBa and 11.4% in the CBT group. The therapeutic alliance was rated as better by both therapists and participants in the MoBa vs. the CBT group on all three factors: agreement on tasks of therapy (mean difference: 0.24 for therapists and 0.22 for patients); agreement on goals of therapy (0.24 and 0.02); and affective bond (0.05 and 0.16), although no difference was statistically significant.

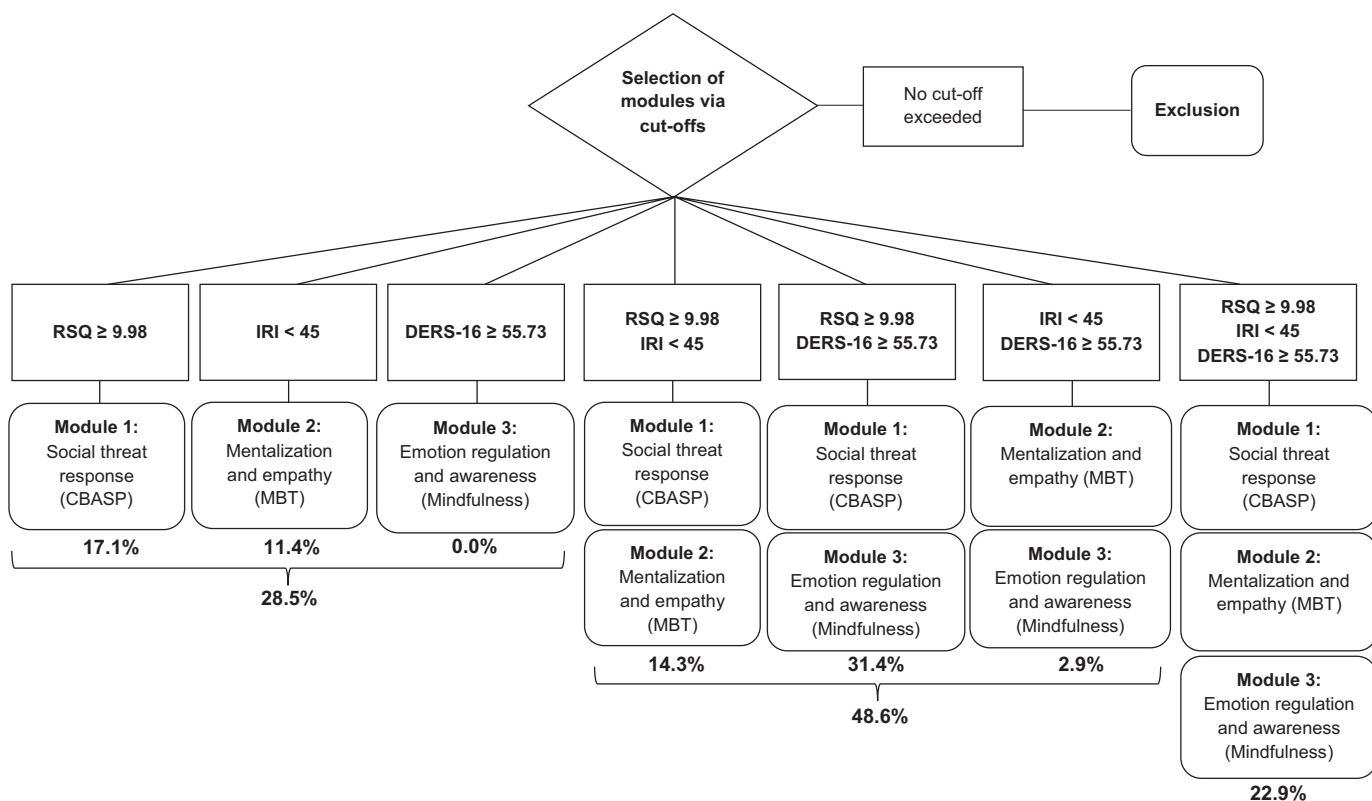


Figure 2 Selection of modules according to the evidence-based algorithm. RSQ – Rejection Sensitivity Questionnaire, IRI – Interpersonal Reactivity Index, DERS-16 – Difficulties in Emotion Regulation Scale-16, CBASP – cognitive behavioral analysis system of psychotherapy, MBT – mentalization-based therapy.

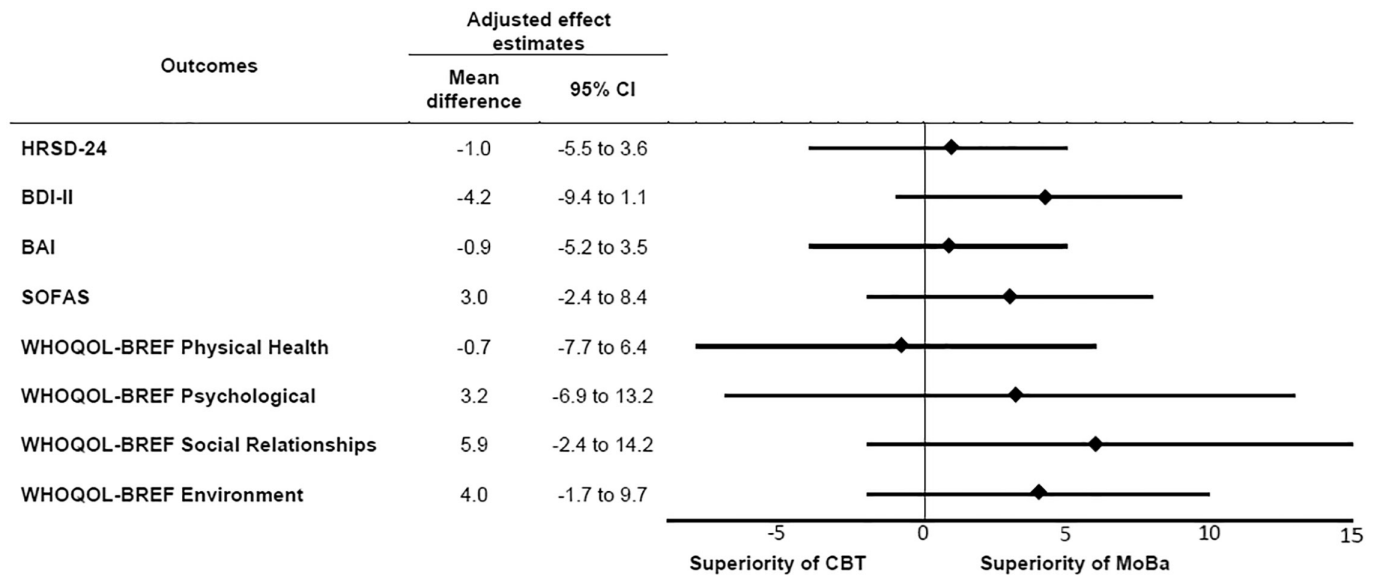


Figure 3 Estimated mean differences between algorithm-based modular psychotherapy (MoBa) and standard cognitive-behavioral therapy (CBT) for measures of clinical efficacy, adjusted for depression type. HRSD-24 – 24-item Hamilton Rating Scale for Depression, BDI-II – Beck Depression Inventory-II, BAI – Beck Anxiety Inventory, SOFAS – Social and Occupational Functioning Assessment Scale, WHOQOL-BREF – World Health Organization Quality of Life - Brief Version.

Patients in the MoBa group completed homework more often than in the CBT group (89.6% vs. 71.0%). Therapists reported more time problems in MoBa compared to CBT sessions (31.4% vs. 18.6%).

Efficacy

After 16 weeks of treatment, the mean HRSD-24 score was 17.2 (95% CI: 14.1-20.4) in the MoBa group and 17.4 (95% CI: 14.3-20.5) in the CBT group. Using the linear regression model, we found an estimated mean difference of -0.2 (95% CI: -4.6 to 4.2). After adjusting for the depression type, the estimated mean difference was -1.0 (95% CI: -5.5 to 3.6). So, concerning the primary outcome, there was a non-significant superiority of MoBa over CBT (see Figure 3).

The response rate was slightly higher in the MoBa than the CBT group (35.3% vs. 31.4%; OR=1.2, 95% CI: 0.4-3.2). However, MoBa patients were nearly three times as likely to experience remission at the end of therapy (29.4% vs. 11.4%, OR=3.2, 95% CI: 0.9-11.6).

Secondary efficacy outcomes showed a non-significant superiority of MoBa over CBT, with a mean difference (after adjusting for the depression type) of -4.2 (95% CI: -9.4 to 1.1) for BDI-II, of -0.9 (95% CI: -5.2 to 3.5) for BAI, of 3.0 (95% CI: -2.4 to 8.4) for SOFAS, of 3.2 (95% CI: -6.9 to 13.2) for WHOQOL-BREF Psychological, of 5.9 (95% CI: -2.4 to 14.2) for WHOQOL-BREF Social Relationships, and of 4.0 (95% CI: -1.7 to 9.7) for WHOQOL-BREF Environment. The only exception was WHOQOL-BREF Physical Health, which showed a non-significant superiority of CBT (mean difference: -0.7, 95% CI: -7.7 to 6.4) (see Figure 3).

Among mechanism-based outcomes, MoBa patients showed a significantly higher post-treatment effect on social processes/empathy after adjusting for the depression type, with an estimated

mean difference of 1.9 (95% CI: 0.0-3.8, $p<0.05$) in the IRI score compared with the CBT group. This latter group actually showed an exacerbation on this domain at post-treatment (see Table 2). The adjusted effect estimates also favored MoBa for the other two mechanism-based outcomes, but not at a statistically significant level: the mean difference, after adjusting for the depression type, was 1.6 (95% CI: -0.7 to 3.9) for the RSQ score, and 1.8 (95% CI: -4.3 to 7.9) for the DERS-16 score (see Table 2).

Overall, 5 of 69 patients (7.2%) deteriorated during treatment, with a mean exacerbation of -6.6 (SD=0.5) HRSD-24 points. Of these, three patients had been randomized to MoBa and two to

Table 2 Estimated mean differences between algorithm-based modular psychotherapy (MoBa) and standard cognitive-behavioral therapy (CBT) for mechanism-based outcomes, adjusted for depression type

	MoBa		CBT		Adjusted effect estimates	
	Adjusted N	mean (SE)	Adjusted N	mean (SE)	Mean difference	95% CI
Rejection Sensitivity Questionnaire (RSQ)						
Baseline	35	16.0 (0.93)	35	15.3 (0.88)		
Post-treatment	34	12.2 (0.81)	33	10.6 (0.81)	1.6	-0.7 to 3.9
Interpersonal Reactivity Index (IRI)						
Baseline	35	44.1 (1.04)	35	43.4 (1.34)		
Post-treatment	34	45.0 (0.68)	35	43.1 (0.65)	1.9	0.0 to 3.8
Difficulties in Emotion Regulation Scale (DERS-16)						
Baseline	35	56.7 (1.95)	35	51.8 (1.92)		
Post-treatment	34	45.5 (2.18)	35	43.7 (2.09)	1.8	-4.3 to 7.9

The significant difference between MoBa and CBT ($p<0.05$) is highlighted in bold prints

CBT.

Safety

Overall, 44 adverse events occurred during the trial, including symptom exacerbation or occurrence of new symptoms in eight cases, passive suicidal thoughts in eight cases, and problems in the patient-therapist relationship in four cases. The number of adverse events was substantially lower in the MoBa group (15; 34.1%) than in the CBT group (29; 65.9%), corresponding to an average number of 0.43 events per MoBa patient, and 0.83 events per CBT patient. No severe adverse events were reported.

DISCUSSION

This is the first randomized controlled trial to investigate the feasibility, acceptability and efficacy of an algorithm-based selection of treatment modules complementing standard CBT. The algorithm was derived from a mechanistic model of the sequelae of early life adversity, and therapists were asked to select, in the individual patients, the appropriate modules on the basis of a baseline assessment of those sequelae.

In a highly burdened sample of early traumatized patients with mostly persistent or recurrent depression and psychiatric comorbidities, the modular approach proved highly acceptable. Both patients and therapists reported high or very high post-session satisfaction more frequently with MoBa than with CBT. The therapeutic alliance was rated as better by both patients and therapists in the MoBa vs. the CBT group regarding all its key elements (agreement on tasks of therapy, agreement on goals of therapy, and affective bond).

MoBa therapists reported more time pressure, very likely because of the challenge to integrate the additional modules within a small number of 20 sessions. On the other hand, patients in the MoBa group completed homework more often and reported less difficulties in their relationship to the therapist than those in the CBT group.

Very few of these severely affected patients dropped out or deteriorated. Patients receiving MoBa reported a substantially lower number of adverse events than those in the CBT group. No serious adverse event occurred.

The MoBa approach was associated with a superiority over standard CBT on both the primary (HRSD-24 score at post-treatment) and almost all of the secondary (self-rated depressive and anxiety symptoms, clinician-rated social and occupational functioning, self-rated quality of life) efficacy outcomes. However, no difference reached statistical significance, most likely due to the small sample size.

Patients in the modular treatment arm were nearly three times as likely to show post-treatment remission (29.4% vs. 11.4%, OR=3.2). This finding provides a preliminary support to the usefulness of a modular mechanism-based approach aimed to personalize psychotherapy^{9,45}, in order to address the substantial interindividual heterogeneity in treatment effects among depressed patients⁴⁶⁻⁵².

Our treatment algorithm was based on the baseline assessment

of three early trauma-related transdiagnostic mechanisms: social threat response, hyperarousal, and social processes/empathy. There was a significant differential treatment effect regarding social processes/empathy, as MoBa patients reported pre-post improvements while CBT patients showed an exacerbation on this domain. Interestingly, the mentalizing module addressing this domain was the only one including elements not derived from a third-wave CBT, but from a psychodynamic approach³⁶. The adjusted effect estimates also favored MoBa on the other two mechanism-based outcomes, although the difference did not reach a statistically significant level, again likely due to the small sample size.

Statistical analyses were limited to overall comparisons of MoBa vs. CBT, since tests comparing different modules were not sufficiently powered. While the modules were selected based on an evidence-based algorithm, the sequencing of the strategies within modules were based on the therapists' individual case conceptualizations. There is no reliable evidence to support a data-driven decision algorithm for sequencing as yet. However, monitoring and feedback systems have been reported to increase the efficacy of psychotherapies by further personalizing and adapting interventions to the patients' response^{53,54}. These will be tested in a future confirmatory trial.

Since both interventions were provided by the same therapists, some degree of involuntary treatment diffusion might have occurred^{55,56}. Therefore, separate therapists being trained in and delivering only one intervention will have to be used in the future to systematically prevent this effect.

Up to now, little is known about how interventions should be structured in modular psychotherapies⁵⁷. Different from most practicing clinicians who follow eclectic treatment approaches according to their expertise and intuition⁵⁸, empirically based rules are needed to arrive at replicable treatment standards. This is the first study which applied a personalized decision-making principle of module selection based on an algorithm derived from a mechanistic model. It is notable that this model was informed by the RDoC approach, which does not happen frequently in clinical trials and practice.

Although MoBa randomized participants had characteristics associated with greater treatment resistance than those receiving standard CBT, the modular approach proved to be feasible, safe and effective, showing advantages related to patients' and therapists' satisfaction and several clinical outcomes. While this seems highly promising as a distinct pathway to achieve personalization, further evaluation will be needed in a fully powered confirmatory trial.

To account for the results of this proof-of-concept trial, an optimized design will have to incorporate more therapy sessions, include a monitoring system, and involve patients in standardized shared decision-making to sequence modules. In the future, a combination of theory- and data-based algorithms may be optimal, with machine learning analyses of actuarial data to build replicable processes and outputs.

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