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Efficacy of Acceptance and Commitment Therapy in Daily Life in Early Psychosis: Results from the Multi-Center INTERACT Randomized Controlled Trial

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Keywords

Acceptance and commitment therapy · Ecological momentary intervention · Blended care · mHealth · Early psychosis

Abstract

Introduction/Objective: This study aimed to investigate efficacy of Acceptance and Commitment Therapy in Daily Life (ACT-DL), combining face-to-face therapy with an Ecological Momentary Intervention (EMI), in addition to treatment as usual (TAU) for psychotic distress, in comparison to TAU. *Methods*: Individuals aged 15–65 years with clinically established ultra-high risk or first episode of psychosis were randomly assigned to TAU or ACT-DL+TAU. ACT-DL+TAU consisted of 8 ACT-sessions augmented with an EMI-app. The primary outcome was psychotic distress assessed with the Comprehensive Assessment scale of At Risk Mental State (CAARMS) at post-intervention and 6- and 12-month follow-up. Secondary outcomes were functioning, symptom severity, and momentary psychotic distress. We performed multivariate mixed models according to intent-to-treat principles. ***Results:*** Between June 1, 2015 and December 31, 2018, 668 participants were referred, of whom 148 were randomized to ACT-DL+TAU (n = 71) or TAU (n = 77). One hundred and fifteen (78%) provided primary outcome data at least at one follow-up assessment. There was no evidence of greater reduction in the primary outcome measure CAARMS distress in ACT-DL+TAU compared to TAU ($\chi^2(3) = 2.36$; $p = 0.50$). However, out of the tested secondary outcomes, global function-

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ing ($\chi^2(3) = 9.05$; $p = 0.033$), and negative symptoms ($\chi^2(3) = 19.91$; $p<0.001$) improved in ACT-DL+TAU compared to TAU, as did momentary psychotic distress ($\chi^2(3) = 21.56$; $p < 0.001$). ***Conclusions:*** INTERACT did not support a significant effect of ACT-DL over TAU on the primary outcome measure of psychotic distress as assessed with the CAARMS. Although significant improvements were found for some secondary outcome measures, further replication studies are needed to confirm the strength and specificity of these effects.

Introduction

Treatment in the early stages of psychosis, including both ultra-high risk (UHR) and first-episode psychosis (FEP) [1–4], is crucial to prevent transition to more severe stages of illness. While most studies have targeted transition to psychotic disorder or reduction of positive symptoms as their main outcome, distress associated with psychotic symptoms has been identified as a major driver of illness [5]. Also, when investigated at a momentary level using experience sampling methodology (ESM), psychotic distress is prominently present in the early stages of psychosis [6, 7]. Furthermore, treatment should target a wider range of symptoms including negative and affective symptoms, while also improving global and social functioning [8].

A comprehensive meta-analysis of preventive interventions for individuals at ultra-high risk for psychosis found no effects of either psychological or pharmacological interventions on psychotic distress, nor on affective symptoms, negative symptoms, and functioning [9], calling for more treatments for these. Acceptance and Commitment Therapy (ACT), a third-wave behavioral therapy aimed at enhancing individuals' psychological flexibility, may help patients to handle distress [10]. While ACT components targeting acceptance are likely to be effective in attenuating distress, ACT components targeting commitment may enhance reward-related motivated action. There is good evidence for the feasibility and acceptability of ACT in people with psychosis [11, 12]. In addition, while one systematic review provided cautious support for a positive effect of ACT on psychotic symptoms [13], meta-analytic evidence on a small number of studies found limited effects in individuals with an established psychotic disorder [14]. We therefore developed ACT in Daily Life (ACT-DL) for enhancing the therapeutic effects of ACT under real-world conditions [15–17]. ACT-DL builds on the principles of Ecological Momentary Interventions (EMI) [16], providing treatment in real-time. While pilot studies provided evidence on acceptability and feasibility of ACT-DL in both a clinical sample of patients with mental health disorders [18], as well as in emerging adults with subthreshold levels of depression and psychosis [19], robust, trial-based evidence on its effects in the early stages of psychosis is lacking.

The aim of the current INTERACT study was to test the efficacy of ACT-DL in reducing psychotic distress (primary outcome) as well as in reducing intensity of psychotic symptoms, general psychopathology, and negative symptoms and improving global and social functioning (secondary outcomes), and in improving momentary psychotic distress, psychotic experiences and mood (secondary outcomes measured with the ESM) at post-intervention and 6- and 12-month (for non-ESM outcomes only) follow-ups in patients with UHR and FEP. In an a priori planned subgroup analysis, the effects of ACT-DL on the primary outcome in UHR compared with FEP individuals was investigated. In a more exploratory a priori planned sensitivity analysis, we investigated whether the reduction in psychotic distress is greater for TAU including cognitive behavior therapy for psychosis (CBTp) compared to TAU as well as for ACT-DL+TAU compared to CBTp+TAU.

Our objectives that aim to examine processes measuring mechanisms of change as well as to assess acceptability and treatment engagement [20] will be addressed in subsequent papers [21].

Materials and Methods

Study Design and Participants

The study was a multi-center single-blind randomized controlled trial (RCT). Individuals within the early stages of psychosis were recruited from secondary mental health services in five regions in the Netherlands and Belgium: (1) Amsterdam (Academic Medical Centre, Arkin Basis GGZ), (2) The Hague (Parnassia, PsyQ), (3) Maastricht/Eindhoven (Mondriaan, Virenze, GGZE), (4) Flemish-Brabant (UPC KU Leuven, VDIP Antwerp, Sint-Annendael, PCM Mortsel), and (5) East/West Flanders (OLV Brugge, Karus Melle, VDIP Sint Niklaas). Individuals were referred to the study by their treating clinician. A week after being fully informed by a researcher, informed consent was obtained, after which full eligibility assessment was conducted. Inclusion criteria were: age 15–65 years; meeting criteria for UHR (without prior use of antipsychotic medication for psychotic symptoms) or FEP (onset within last 3 years) as assessed by the Comprehensive Assessment of At Risk Mental State (CAARMS) [1] and Nottingham Onset Schedule [22]; sufficient command of the Dutch language for outcome assessment and receiving the intervention; and ability to provide written informed consent. Exclusion criteria included a primary diagnosis of alcohol/substance abuse or dependence, as-

sessed with the Mini-International Neuropsychiatric Interview [23], and severe endocrine, cardiovascular, or brain disease. The study received ethical approval from the MERC at Maastricht University Medical Centre (MUMC), the Netherlands (reference: NL46439.068.13) and the University Clinic Leuven, Belgium (reference: B322201629214). The trial was prospectively registered in the Netherlands Trial Register (NTR4252). The trial protocol has been published elsewhere [20], and the study was post-registered on the open science framework[1] (see Supplement 1). The study was set up and described according to the methodological recommendations for trials of psychological interventions as outlined by Guidi et al. [24].

Randomization and Masking

Participants were randomized (1:1) by an independent researcher to the experimental condition (ACT-DL+TAU) or the control condition (TAU). Randomization was at the level of the individual participant through a computer-generated sequence devised by this same researcher following informed consent, full eligibility assessment, and baseline assessment of outcome measures. Block randomization was carried out in blocks of 6 participants, with stratification for the five regions and for group (UHR and FEP, expecting a 50:50 ratio). Trained researchers blind to the allocation of participants conducted post-intervention and follow-up assessments. To ensure blinding, each of the five regions had a dedicated contact person for any questions regarding the procedure, who was not involved in any testing in that region. Any breaks in blinding were documented in a blinding-checklist, in which the assessors reported whether they had suspicions and/or whether they were sure about the intervention allocation of the participant, after which they were asked to indicate the suspected condition. In case of deblinding, another researcher was allocated to complete the next (set of the) assessment(s).

Procedures

Therapy in both conditions was provided at the mental health service where individuals were enrolled. Participants allocated to TAU received standard care delivered according to national service guidelines and protocols by their responsible clinician. Standard mental health care included manualized CBTp at some sites. Individuals in the ACT-DL condition received TAU with the exception of manualized CBTp.

ACT-DL consisted of eight manualized ACT sessions (45–60 min), administered face-to-face by a trained clinician and an ACT-DL EMI to apply the learned skills in their daily lives. After a psycho-education session, patients received six ACT sessions based on a modified version of ACT for people with psychosis [10, 11, 25, 26], in the final session all six components were integrated.

The ACT-DL EMI prompted participants at 8 semi-random moments per day for 3 days after each session (starting from session two), with a brief questionnaire on their current mood, psychotic experiences and activities, as well as providing an exercise or metaphor of the ACT component covered in the previous session. In addition, participants could do ACT exercises at moments when they were most needed. After completion of the intervention period, participants no longer had access to the app (see our study protocol [20] and Vaessen et al., 2019 [15] for more information).

Treatment fidelity was rated based on a random selection of audiotapes of three training sessions per participant using an adherence checklist covering all core ACT and ACT-DL app components within each session [20]. Ratings were based on the extent to which the component was addressed in each session (0 no, 1 to some extent, 2 yes), with 7 components to score in the sessions on contact with the present moment and values, and 6 components in all other sessions. We calculated a mean fidelity score (range 0–12.6).

Data were collected at clinical sites of the five regions introduced above. Assessments were conducted before randomization ("baseline"), after the 8-week intervention period ("post-intervention"), and after 6-month (all outcomes) and 12-month follow-up. Secondary outcomes using the ESM were assessed at baseline, post-intervention, and 6-month follow-up. We conducted regular reliability meetings to assess interrater reliability for audiotaped scores on all clinical interviews, including the CAARMS (intensity and frequency score), SOFAS (total score), BPRS (total and subscale scores), and BNSS (total score). Intra-class correlation coefficients were calculated to examine interrater reliability using the iccNA command in R.

Choice of Primary Outcome Measure

The primary outcome was distress associated with psychotic experiences measured with the sum distress score (range 0–400) of the CAARMS positive symptom subscales [1]. The CAARMS is a semi-structured interview gathering detailed information on the intensity, frequency, and emotional distress of various positive symptoms to detect whether individuals meet UHR or FEP criteria, with good psychometric properties [1]. It has been used to assess psychotherapy-induced changes in psychotic distress in both UHR and FEP individuals [27], thus providing a high-quality instrument that can be used across the different stages of early psychosis. The instrument has been widely adopted and is freely available in different languages. Thorough clinical training before using the instrument is necessary.

Secondary Outcomes

Secondary outcomes included global and social functioning assessed with the SOFAS [28] and SFS [29], and symptom severity assessed with the BPRS [30] and BNSS [31]. Other secondary outcomes were measured with the ESM and included momentary psychotic distress (operationalized as the association between momentary psychotic experiences and momentary negative affect), momentary intensity of psychotic experiences, and momentary positive affect and negative affect (see Supplementary Table 1). ESM is a structured, time-sampling diary technique used to measure mood, symptoms, and context at 10 semi-random times per day over a period of 6 consecutive days using an established ESM data collection protocol on a smartphone-based app [32, 33]. Any serious adverse events were recorded throughout the entire study period and were reported to the accredited MERC. Details on the operationalization of the outcomes are reported in our post-registration report[1].

[1] The current study was post-registered on the Open Science Framework (OSF), meaning that we registered our analysis plan after we had collected data, however before we had any access to the data. The main post-registration for the INTERACT study is available here https://osf.io/du2bn/?view_only=ec22ed02651441349e1bb1242cfc712c.The post-registration for the current study is embedded as a file within the main registration and can be accessed here https://osf.io/5qfwe/? view_only=4062ccf54b0d4161a0e481aa80e76e78.

Statistical Analysis

Power simulation in R indicated that a sample size of 150 participants (75 per arm) would have 92% power to detect a medium effect size of $d = 0.5$ at (at least) one of the post-intervention and follow-up time points when testing our primary hypothesis at $\alpha = 0.05$, while allowing for an expected attrition rate of 31% to follow-up.

Statistical analyses were conducted using Stata (version 14.2) and were specified in the published protocol [20] and post-registered analysis plan. The data were analyzed according to intention-to-treat principles.

Multivariate mixed models were fitted for primary and secondary outcomes separately with scores at post-intervention and 6-month and 12-month follow-up as the dependent variable. The independent variables included condition, time, group status (UHR or FEP), region, baseline score (grand-mean centered), a baseline score × time interaction, and a condition × time interaction. An omnibus test of no difference between the two conditions was performed at all three time points (Wald-type test with df = 3 and $\alpha = 0.05$). Only if statistically significant, the three time-specific contrasts were examined (each tested at $\alpha = 0.05$), precluding the need for adjusting for multiple testing at the level of time-specific contrasts. Within-subject clustering of repeated measures was taken into account by allowing residuals within subjects to be correlated with a completely unstructured variance-covariance matrix.

In the models with ESM outcomes, momentary psychotic experiences, positive and negative affect were included as dependent variables with the same independent variables as previously described. In the analysis of momentary psychotic distress (defined as the association between momentary psychotic experiences and negative affect), negative affect was the dependent variable and momentary psychotic experiences (person-mean centered), a momentary psychotic experiences × time interaction, a momentary psychotic experiences × condition interaction, and a momentary psychotic experiences × time × condition interaction were added as additional independent variables to the model. For these models, an additional level of nesting was added with multiple ESM observations (level 1) being nested within time points (post-intervention, 6-month follow-up) (level 2) nested within subjects (level 3). We added level-3 random intercepts (and person-mean centered slopes for our model testing momentary psychotic distress) to these models, and, within each level-2 time point, level-1 within-subject residual errors were modelled to have an autoregressive structure (of the exponential type), which allowed these models to account for unequally spaced time values.

To test whether the effect of condition on CAARMS distress score differed between UHR and FEP participants, we added time × group, condition × group, and condition × time × group interactions to the model (planned subgroup analysis). Again, an omnibus test of no group difference (UHR vs. FEP) in the condition effect (which is the difference between ACT-DL+TAU vs. TAU) at all three time points was performed and, only if statistically significant, time-specific contrasts were examined. In a more exploratory sensitivity analysis, we probed our findings further to investigate whether the effect of ACT-DL+TAU versus TAU (difference 1) on CAARMS distress scores was different from the effect of ACT-DL+TAU versus CBTp (difference 2) by including a 3-level factor variable for condition in the model. Also, in this model, we performed an omnibus test of no difference between ACT-DL+TAU and TAU versus ACT-DL+TAU and CBTp at all three time points before looking into time-specific contrasts.

All models were fitted using restricted maximum likelihood (REML) estimation, allowing for the use of all available data under the assumption that data is missing at random and that all variables associated with missing values are included in the model. To test for the latter, we fitted multilevel logistic regression models to examine if baseline characteristics were associated with missingness in the primary outcome or with missingness in secondary ESM outcomes at follow-up. If significant, these characteristics were added to the models as covariates.

Results

As shown in Figure 1, of the 668 individuals identified by clinicians, 196 were assessed for eligibility (Supplementary table 2). Of these, 148 participants were randomized to ACT-DL+TAU ($n = 71$) or to TAU ($n = 77$ with $n = 27$ receiving CBTp+TAU). Attrition rates for the primary outcome at post-intervention assessment were 21 (30%) participants in ACT-DL+TAU and 17 (22%) in TAU. The attrition rate was higher than expected at 6-month and 12-month follow-up (see Fig. 1).

Table 1 shows baseline sample characteristics. The sample included 78 individuals with UHR and 70 with FEP and was nearly equally divided between men and women, with a slightly larger proportion of women in ACT-DL+TAU compared to TAU. The majority of participants lived with others, were employed or student, and did not obtain higher education. Almost 40% of participants in each condition were from an ethnic minority group.

The treatment fidelity checklist was completed for 37 participants and scored for 89 recorded sessions. Findings on treatment fidelity showed very good adherence to the ACT-DL manual, with an overall mean fidelity score of 10.7 (SD = 1.5; range 6.5–12.5). Patients participated on average in 6 (SD 3) out of 8 sessions. The deblinding checklist was administered for $n = 274$ interviews. While in $n = 24$ of these interviews, the assessors reported to be sure about the condition to which participants were randomized, this was only true for $n = 22$ interviews. We did not have deblinding data available for $n = 4$ interviews. Interrater reliability analyses yielded the following scores: 0.79–0.96 for CAARMS intensity and 0.81–0.93 for frequency scores, 0.67 for the SOFAS, 0.84–0.95 for BPRS (sub)scales, and 0.87 for the BNSS, showing sufficient agreement in all scales. We found no association between baseline variables, condition, and missingness of the primary outcome measure. However, as global functioning (SOFAS) was significantly associated with missingness in secondary ESM outcome measures, analyses on these

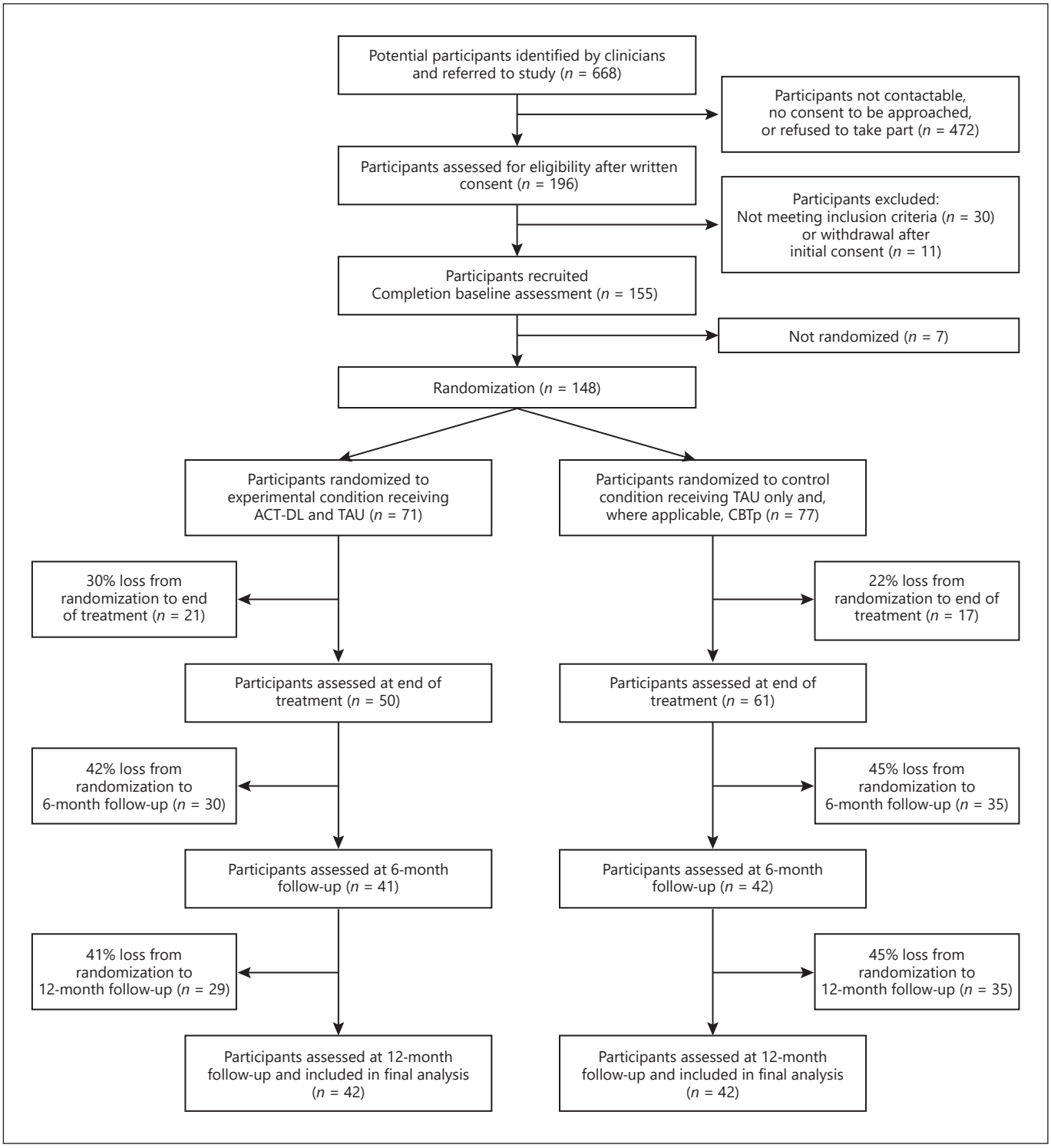

Fig. 1. Study flowchart.

outcomes were controlled for this variable (see Supplementary Table 3).

Table 2 shows descriptive statistics, adjusted mean differences with 95% confidence intervals, and *p* values for primary and secondary outcomes (see Supplementary Figure 1 for Cohen's *d* effect sizes). There was no evidence of a greater reduction in CAARMS distress in ACT-DL+TAU compared to TAU ($\chi^2(3) = 2.36$; $p = 0.50$). However, ACT-DL+TAU showed greater improvement in several secondary outcomes compared to TAU. ACT-DL+TAU showed greater improvement in global functioning assessed with the SOFAS ($\chi^2(3) = 9.05$; $p = 0.03$) at post-intervention and 6-month and 12-month follow-up, but failed to reach statistical significance in social functioning assessed with the SFS ($\chi^2(3) = 7.49$; $p = 0.06$). Moreover, greater reductions in BPRS symptom scores were found in ACT-DL+TAU for the total ($\chi^2(3) = 14.44$; $p = 0.002$) and affective ($\chi^2(3) = 8.49$; $p = 0.04$) symptom scale at 6-month follow-up as well as for the negative symptom scale ($\chi^2(3) = 19.91$; $p < 0.001$) at 6- month and 12-month follow-up (see Supplementary Figure 2). In addition, compared with TAU, ACT-DL+TAU was associated with greater reductions in negative symptoms measured with the BNSS ($\chi^2(3) = 15.96$; $p = 0.001$) at 6-month and 12-month follow-up. There were no significant effects on momentary positive affect, negative affect, and psychotic experiences. However, as shown in Table 2, there was strong evidence of greater reductions in momentary distress associated with psychotic experiences in ACT-DL+TAU compared to TAU ($\chi^2(3) = 21.56$; $p < 0.001$). Specifically, this showed that the reduction in the association between momentary psychotic experiences and momentary negative affect was greater in ACT-DL+TAU than TAU at both post-intervention (adjusted mean difference, –0.21, 95% CI –0.40 to –0.02; $p = 0.03$) and 6-month follow up (adjusted mean difference –0.36, 95% CI –0.58 to –0.14; $p = 0.002$). When excluding those interviews with missing data on the blinding-checklist ($n = 4$) or where deblinding occurred ($n = 22$), the condition × time effect was no longer significant for the BPRS affect scores ($\chi^2(3) = 7.35$; $p = 0.06$). All other results remained identical. Supplementary table 4 provides an overview of number of participants who displayed deterioration in scores after treatment in the two treatment conditions.

The planned subgroup analysis comparing the between-condition effect in UHR versus FEP individuals yielded no significant results (Table 3 and Supplementary Fig. 3).

Table 1. Baseline demographic and clinical characteristics of the intention-to-treat population

Characteristic	Total ($n = 148$)					TAU only ($n = 77$)					ACT-DL+TAU ($n = 71$)				
Age, mean, *SD*, range	25	6	15–47			24	6	15–43			26	6	16–47		
Female, *n*, %	72	49%				30	39%				42	59%			
Living alone, *n*, %	25	17%				12	16%				13	18%			
Employment status, *n*, %															
Employed (full-time or part-time)	36	25%				18	24%				18	26%			
Unemployed (non-structured)	62	42%				36	47%				26	37%			
Student	36	25%				17	22%				19	27%			
Other	12	8%				5	7%				7	10%			
Higher education	50	34%				23	30%				27	39%			
Ethnic minority	56	38%				30	39%				26	37%			
Medication use[a, b], *n*, %															
Antidepressants	29	20%	21	27%	8	11%	18	23%	16	37%	2	6%	11	16%	5	15%	6	17%
Sleep medication	15	10%	4	5%	11	16%	7	9%	2	5%	5	15%	8	11%	2	6%	6	17%
Anxiolytics	28	19%	6	8%	22	31%	10	13%	3	7%	7	21%	18	26%	3	9%	15	42%
Antipsychotics[c]	66	45%	3	4%	63	90%	34	44%	3	7%	31	91%	32	46%	0	0%	32	89%
Other psychotropic medication	7	5%	3	4%	4	6%	4	5%	2	5%	2	6%	3	4%	1	3%	2	6%
FEP[d], *n*, %	70			47%			34			44%			36			51%		

FEP, first episode of psychosis. [a] Data for all participants, UHR and FEP participants separately. [b] Individuals could be prescribed multiple psychotropic medications. [c] Antipsychotics for UHR individuals were prescribed at dosages too low to function as an antipsychotic agent. [d] FEP versus ultra-high risk for psychosis (UHR).

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Table 2. Primary and secondary outcomes at baseline, post-intervention, and 6-month and 12-month follow-up

Outcome	Time	TAU only[a]			ACT-DL+TAU[a]			Adjusted mean differences at follow-up time points[b]				Omnibus test[c]		
		Mean, SD, *n*			Mean, SD, *n*			Mean, SE		95% CI	*p* value	$\chi^2(3)$	*p* value	*n*
CAARMS	Base	201.25	83.92	75	205.57	82.84	70							
	Post	89	86.51	58	76.08	79.51	50	−6.10	14.12	−33.77; 21.58	0.67	2.36	0.50	115
	FU6	68.95	81.14	42	77.68	76.23	41	9.90	15.98	−21.43; 41.23	0.54			
	FU12	76.59	80.06	41	64.34	78.57	41	−11.31	17.84	−46.28; 23.66	0.53			
SFS	Base	107.99	9.45	74	109.21	8.05	68							
	Post	109.33	8.40	56	112.08	8.08	48	2.82	1.19	0.48; 5.16	0.02	7.49	0.06	112
	FU6	109.63	9.01	38	112.66	9.37	36	3.63	1.54	0.61; 6.65	0.02			
	FU12	110.58	9.27	36	114.88	9.85	39	2.10	1.73	−1.30; 5.49	0.23			
SOFAS	Base	39.70	10.56	77	38.44	10.20	71							
	Post	50.92	12.75	60	53.88	10.84	50	5.03	2.15	0.81; 9.24	0.02	**9.05**	**0.03**	118
	FU6	52.17	14.15	42	58.15	10.33	41	5.98	2.40	1.27; 10.68	0.01			
	FU12	53.45	13.79	42	59.63	10.32	41	6.02	2.38	1.36; 10.68	0.01			
BPRS total	Base	42.01	8.92	77	39.47	7.73	71							
	Post	37.62	8.95	61	36.97	9.06	50	0.53	1.42	−2.26; 3.32	0.71	**14.44**	**0.002**	119
	FU6	39.23	8.07	42	33.80	7.28	40	−5.40	1.61	−8.55; −2.24	0.001			
	FU12	37.84	11.15	41	34.92	9.13	42	−3.06	2.22	−7.41; 1.29	0.17			
BPRS affective	Base	13.30	4.71	77	12.55	4.44	71							
	Post	11.26	4.86	61	10.41	4.57	50	−0.66	0.78	−2.18; 0.87	0.40	**8.49**	**0.04**	119
	FU6	11.52	4.98	42	9.55	3.59	40	−2.34	0.82	−3.95; −0.74	0.004			
	FU12	10.80	4.65	41	9.60	3.31	42	−1.27	0.89	-3.01; 0.46	0.15			
BPRS activation	Base	9.85	3.30	77	9.13	2.19	71							
	Post	8.75	2.72	61	9.14	2.52	49	0.84	0.44	−0.02; 1.70	0.06	4.92	0.18	118
	FU6	9.43	3.29	42	8.62	1.84	39	−0.48	0.53	−1.53; 0.56	0.36			
	FU12	10.00	3.83	36	9.85	2.89	39	−0.10	0.79	−1.65; 1.45	0.90			
BPRS positive	Base	10.2	3.49	77	9.34	3.32	71							
	Post	9.29	2.93	60	9.18	4.02	50	0.26	0.56	−0.84; 1.37	0.64	0.80	0.85	118
	FU6	8.81	3.66	42	8.33	3.40	40	−0.19	0.64	−1.44; 1.07	0.77			
	FU12	9.24	3.67	41	9.12	4.14	42	0.03	0.78	−1.49; 1.55	0.97			
BPRS negative	Base	8.65	3.00	77	8.45	2.68	71							
	Post	8.46	3.31	61	8.42	2.89	50	−0.06	0.44	−0.92; 0.80	0.89	**19.91**	**<0.001**	119
	FU6	9.48	2.87	42	7.72	2.48	39	−1.67	0.56	−2.76; −0.58	0.003			
	FU12	9.47	3.66	39	7.22	1.72	41	−2.46	0.62	−3.67; −1.25	<0.001			
BNSS	Base	22.21	12.96	76	17.30	11.93	71							
	Post	17.14	14.37	61	15.68	13.65	50	0.12	1.86	−3.52; 3.75	0.95	**15.96**	**0.001**	118
	FU6	20.10	15.43	42	11.00	9.11	41	−8.00	2.39	−12.68; −3.32	0.001			
	FU12	17.05	14.14	41	9.56	11.29	42	−5.70	2.50	−10.60; −0.79	0.02			
ESM[d] momentary NA~PE[e]	Base	0.64	0.06	76	0.76	0.07	71							
	Post	0.71	0.08	52	0.45	0.10	44	−0.21	0.10	−0.40; −0.02	0.03	**11.11**	**0.004**	103
	FU6	0.81	0.12	39	0.41	0.16	30	−0.36	0.11	−0.58; −0.14	0.002			

Table 2 (continued)

Outcome	Time	TAU only[a]			ACT-DL+TAU[a]			Adjusted mean differences at follow-up time points[b]				Omnibus test[c]		
		Mean, SD, *n*			Mean, SD, *n*			Mean, SE	95% CI	*p* value	$\chi^2(3)$	*p* value	*n*	
ESM momentary PE	Base	2.18	0.92	76	2.11	0.97	71							
	Post	1.96	0.92	52	1.99	0.99	44	0.12	0.16	–0.20; 0.43	0.47	3.64	0.16	103
	FU6	2.08	0.96	39	1.64	1.05	30	.01	0.16	–0.31; 0.33	0.95			
ESM momentary PA	Base	3.80	0.90	76	3.93	1.07	71							
	Post	4.10	1.18	52	4.32	1.19	44	0.16	0.17	–0.17 to 0.49	0.33	11.85	0.003	103
	FU6	4.05	0.98	39	4.40	1.39	30	–0.17	0.18	–0.51 to 0.17	0.33			
ESM momentary NA	Base	2.64	1.14	76	2.46	1.05	71							
	Post	2.38	1.21	52	2.35	1.18	44	0.12	0.18	–0.23 to 0.48	0.51	7.37	0.025	103
	FU6	2.58	1.11	39	1.83	1.41	30	–0.11	0.19	–0.47 to 0.26	0.56			

CAARMS, Comprehensive Assessment of At Risk Mental State; SFS, Social Functioning Scale; SOFAS, Social and Occupational Functioning Scale; BPRS, Brief Psychiatric Rating Scale; BNSS, Brief Negative Symptom Scale; ESM, Experience Sampling Method; SD, standard deviation; Stand., standardized; CI, confidence interval. [a] Data are sample mean scores (between-subject SD), number of observations. Number of observations differs from the maximum when participants did not complete the measure. [b] Adjusted mean differences are based on a complete-case ITT analysis. [c] Omnibus test of no differences at all three time points (χ^2(df) with 3 degrees of freedom, $\alpha = 0.05$, number of observations in the analysis. [d] Analyses with ESM outcomes were adjusted for SOFAS score at baseline. [e] For momentary psychotic distress, data represent slope coefficients (standard error) expressing the strength of association between momentary negative affect and momentary person-mean centered psychotic experiences.

Likewise, our exploratory analysis comparing ACT-DL+TAU versus TAU with ACT-DL+TAU versus CBTp+TAU did not reach significance (Table 4).

Finally, 5 serious adverse events were reported during the trial, 4 in the TAU condition and 1 in the ACT-DL condition. All of them were classified as being unrelated to treatment.

Discussion

No effect was found of ACT-DL+TAU compared to TAU on the primary outcome measure of psychotic distress in individuals at the early stages of psychosis. However, substantial improvements in the experimental condition were found for some of the secondary outcome measures, that is, for momentary psychotic distress, negative symptoms at 6- and 12-month follow-up, evident in two separate measures, as well as for global functioning at post-intervention and 6- and 12-month follow-up.

The lack of significant findings on psychotic distress seems to be mainly due to the fact that TAU was as successful as ACT-DL+TAU in reducing psychotic distress over time. This is in line with a recent study showing that distress in UHR individuals tended to sharply decline in the first 3 months after inclusion in an intervention trial [34], irrespective of the intervention arm, indicating that distress in these early phases of illness may be ameliorated by just monitoring and having someone to talk to. This seems supported by the literature, as a recent comprehensive meta-analysis, indeed, found no differential effect of any psychological nor pharmacological intervention on psychotic distress in the early phases of psychosis [8]. Furthermore, it fits with recent meta-analyses and systematic reviews showing limited effects of ACT on psychotic symptoms [13, 14], showing that adding an EMI to the ACT intervention is not increasing the effects on psychotic distress. The ACT-DL intervention, including 8 sessions, is in the mid-range of number of sessions used in clinical trials, with numbers ranging from 3 to 16 sessions, and seems representative of the current ACT literature. However, ACT-DL+TAU is associated with larger improvements in self-reported psychotic distress in daily life compared to TAU, a secondary outcome measure. The use of ESM may be particularly helpful in capturing more subtle changes in psychotic distress as it unfolds in daily life, as it provides more fine-grained measures of psychotic distress over different situations and contexts, while minimizing memory biases as well as reducing desirable responding.

Table 3. Planned subgroup analysis of treatment effect on CAARMS distress scores in UHR and FEP individuals at post-intervention and 6-month, and 12-month follow-up

Effects[a]	Time	Coefficient (SE)		95% CI	*p* value	Omnibus test		
						$\chi^2(3)$ [b]	*p* value	*n*
Time × condition	Post	–21.12	19.35	–59.03 to 16.80	0.28			
	FU6	8.59	22.23	–34.97 to 52.15	0.70			
	FU12	–36.75	23.43	–82.68 to 9.17	0.12			
Time × group	Post	–57.83	19.65	–96.35 to –19.31	0.003			
	FU6	–15.17	23.34	–60.91 to 30.57	0.52			
	FU12	–0.52	24.76	–49.05 to 48.01	0.98			
Condition × time × group	Post	34.09	27.90	–20.59 to 88.78	0.22	4.51	0.21	115
	FU6	1.39	32.41	–62.13 to 64.91	0.97			
	FU12	48.09	34.21	–18.97 to 115.15	0.16			

SE, standard error; CI, confidence interval. [a] Effects represent the main effect of condition, group, and the condition × group interaction at various time points within the study. [b] The omnibus test tests whether treatment effects are different in UHR versus FEP individuals across all three time points, reflected by the 3 degrees of freedom in the χ^2test.

In contrast to the null-finding on the primary outcome, we found a consistently stronger effect of ACT-DL+TAU compared to TAU in the models of negative symptoms and global functioning, particularly after 6 and 12 months. Although caution is needed when interpreting secondary outcomes, Zipfel et al. [35] recently argued that especially when testing the effects of new interventions for mental health problems, primary outcomes are not always easy to define. Therefore, secondary outcomes may be very informative to indicate the potential benefits of a novel therapy. In this respect, the finding regarding stronger effects of ACT-DL+TAU compared to TAU is important as both negative symptoms and social functioning are considered the hardest to treat. Although some recent meta-analytic evidence showed small effects of cognitive behaviorally informed interventions on negative symptoms [36, 37] and functioning [36] in individuals with psychosis, two meta-analyses specifically focusing on youth at clinical high risk for psychosis concluded that, currently, no effective treatments are available for either improving functioning [38] or ameliorating negative symptoms [39] in the early stages of psychosis. Yet, negative symptoms are considered the most disabling symptoms [40, 41], being closely associated with lower levels of functioning and higher risk for a more disabling course of illness. Improving both negative symptoms and functioning in these early phases of psychosis is thus very promising for prevention of further deterioration towards severe and recurrent symptoms in later stages of illness. Replication studies are needed to confirm these findings.

The finding that ACT-DL+TAU is particularly relevant for improving negative symptoms and global functioning is in contrast with the current state-of-the-art of ACT therapy in psychosis. One meta-analysis found no effect of acceptance-based interventions on either negative symptoms or functioning [14] and another study did not find a significant difference between second (CBT) and third (ACT) wave interventions on negative symptoms or functioning [36]. However, there are a number of reasons that may explain this discrepancy. First, this is the largest trial examining ACT for psychosis. Previous studies may have been underpowered to detect significant effects. Second, this study used a 12-month follow-up to examine both the immediate and longer-term effects. In contrast, most previous ACT studies used no or a short-term follow-up [14]. Third, this is the first RCT focusing on the early stages of psychosis. Acceptance of distress in these early stages may have contributed to patients being less experientially avoidant in dealing with overwhelming symptoms, which may explain the effects on negative symptoms, while "committed action" may have been particularly instrumental in improving functioning. Fourth, the current study used a blended care intervention, combining face-to-face ACT therapy with the ACT-DL EMI. Although the current study did not evaluate added benefit of ACT-DL over ACT only, the findings of continuous improvement of both functioning and negative symp-

Table 4. ACT-DL versus CBTp exploratory analysis: differences in CAARMS distress scores between ACT-DL+TAU and TAU only versus ACT-DL+TAU and CBTp+TAU at baseline, post-intervention, and 6-month and 12-month follow-up

Time	ACT-DL+TAU			TAU only			Adjusted mean difference[a]				Time	Contrasts[b]			
	Mean	SD	*n*	Mean	SD	*n*	Mean	SE	95% CI	*p* value		$\chi^2(3)$	*p* value	*n*	*p* value
Base	205.57	82.84	70	184.88	78.60	48					Base				
Post	76.08	79.51	50	83.63	86.12	35	2.90	16.40	−29.26 to 35.05	0.86	Post	10.27	0.74	115	0.69
FU6	77.68	76.23	41	59.6	69.33	25	−17.54	18.70	−54.20 to 19.12	0.35	FU6				0.43
FU12	64.34	78.57	41	59.6	60.34	25	−0.34	20.56	−40.63 to 39.95	0.99	FU12				0.26
Time	ACT-DL + TAU			CBTp + TAU											
	Mean	SD	*n*	Mean	SD	*n*									
Base	205.57	82.84	70	230.37	86.61	27									
Post	76.08	79.51	50	97.17	88.38	23	11.60	19.46	−26.55 to 49.75	0.55					
FU6	77.68	76.23	41	82.71	96.56	17	1.46	21.72	−41.11 to 44.02	0.95					
FU12	64.34	78.57	41	103.13	100.16	16	29.72	24.21	−17.72 to 77.16	0.22					

Base, baseline; Post, post-intervention; FU6, 6-month follow-up; FU12, 12-month follow-up; SD, standard deviation; SE, standard error; CI, confidence interval. [a] Reflects the adjusted mean difference between ACT-DL+TAU and TAU only (top) and the adjusted mean difference between ACT-DL+TAU and CBTp+TAU (bottom). [b] Tests whether contrast 1 (ACT-DL+TAU vs. TAU only) is > than contrast 2 (ACT-DL + TAU vs. CBTp + TAU) at all three time points and per time point separately.

toms over time may indicate the added value of the EMI component. Indeed, whereas long-term effects of psychological interventions tend to either stay the same [42] or decline over time [27], a previous EMI in individuals with depression showed a similar pattern of continuous increase in effect up to 24 weeks post-intervention [43]. This might be explained by the fact that EMIs are particularly tuned to applying skills in everyday situations and, thus, towards developing new habits that will increasingly have an effect over time [16]. Further research is needed to demonstrate and disentangle the effects of ACT versus ACT-DL in this population, as well as to identify the contributing components to the long-term effectiveness on negative symptoms and functioning.

The strengths of the current study are the sample size, the use of an active control condition in a subset of participants (including both TAU and structured CBTp), the rigorous trial approach and open science practices (with the study protocol published and the detailed post-registration of the analysis plan), the use of a blended care intervention, the ethnic diversity of the sample, and the wide scope of primary and secondary outcomes, measured, in part, using ESM. The results of this study also need to be interpreted in light of a number of limitations. First, the control condition consists of both non-manualized TAU and TAU including manualized CBTp. Therefore, we did not control for the effect of receiving structured psychotherapy per se in all participants allocated to TAU, nor for the effect of non-specific treatment factors such as attention [24]. However, TAU in the different centers usually included some form of psychotherapy. Second, patients were not allocated to CBTp but received this as part of TAU when it was provided or deemed appropriate in the clinical setting. It is therefore possible that there was some kind of clinical selection in offering CBTp. This could have contributed to the null findings, making the effect in TAU stronger. However, given that only half of the TAU group received CBTp, it is unlikely that this solely explains the negative findings. For the positive findings on the secondary outcomes, a clinical selection bias in CBTp could mean that the actual differences in effect are actually bigger than those reported. Third, the sample included both FEP and UHR individuals. Although both groups represent the early stages of psychosis and are considered temporally and phenomenologically continuous, they do present different stages of illness according to the staging model of psychosis. Indeed, most early intervention studies focus particularly on the UHR group. We randomized the groups stratified by UHR versus FEP, making sure that both groups were

equally distributed over treatment conditions. Furthermore, the planned subgroup analysis showed no differences between UHR and FEP. Fourth, we used two measures to assess negative symptoms in order to increase convergent validity. However, this comes at a cost of incremental validity, where additional measures do not add additional predictive power [44]. However, since similar results were found for both measures, there is no problem of conflicting evidence. We similarly included two measures of global and social functioning. Although both results point in the same direction, only the clinician-rated score of global functioning reached significance. Fifth, whereas use of antipsychotic medication was an exclusion criterion for UHR, most of the FEP were prescribed antipsychotics. We documented this in the sample characteristics. Furthermore, over the course of treatment (including the 6- and 12-month follow-up) individuals could naturally be prescribed antipsychotic medication if clinically indicated, but given the randomization this factor was, as other potential confounders, balanced across conditions. Sixth, ACT-DL included both a face-to-face and an EMI intervention. However, based on this trial, we cannot disentangle the working components. Seventh, the dropout rate was higher than anticipated, in both conditions. The dropout rate post-intervention is slightly higher in the ACT-DL+TAU condition compared to TAU. This may indicate that there may be issues regarding feasibility and acceptability of the intervention for some people (for more information, see van Aubel et al, in press [21]). By the end of the trial, attrition rates increased to over 40% in both conditions, indicating the difficulty of keeping individuals in the early phases of psychosis in treatment as well as in trials. However, the analysis was conducted according to the intention to treat principles in order to minimize attrition bias. Still, since dropout most likely did not occur at random, it is possible that sample characteristics have changed and that the longer-term effects of ACT-DL only apply to a subgroup of patients.

To conclude, the blended care approach of face-to-face ACT with the ACT-DL EMI did not outperform TAU in reducing psychotic distress, the primary outcome measure. However, we did find significant improvements in some secondary outcome measures such as momentary psychotic distress, negative symptoms and functioning in individuals with UHR and FEP. Although these findings may hint towards a potential avenue for treatment in the early stages of illness, they first need to be replicated in follow-up trials in order confirm the strength and specificity of these effects.

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Statement of Ethics

The study received ethical approval from the MERC at Maastricht University Medical Centre (MUMC), the Netherlands (reference: NL46439.068.13) and the University Clinic Leuven, Belgium (reference: B322201629214). Written consent was obtained from each participant prior to assessment and randomization, as detailed in the study protocol (version 12, 18 May 2018). The trial was prospectively registered in the Netherlands Trial Register (NTR4252).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

I.M.G.: conceptualization, methodology, writing – original draft (introduction and discussion), writing – review & editing, visualization, supervision, project administration, funding acquisition. *E.v.A.*: conceptualization, methodology, software, formal analysis, investigation (recruitment and assessment), data curation, writing – original draft (method section and results), writing – review & editing, visualization. *T.V.*: conceptualization, methodology, investigation (recruitment and assessment), writing – review & editing. *H.S.*: conceptualization, methodology, investigation (recruitment and assessment), writing – review & editing. *A.K.*: conceptualization, methodology, investigation (recruitment and assessment), writing – review & editing. *G.L.*: software, formal analysis, writing – review & editing. *W.V.*: methodology, software,

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Data Availability Statement

Deidentified data are available upon request through a data access system, Data cuRation for OPen Science (DROPS), administered via REDCap at the Center for Contextual Psychiatry, KU Leuven.

Interested researchers can submit an abstract, which is subject to review by the research team to ensure there is no overlap with existing projects. Following abstract approval, a variable access request is submitted, and researchers are required to preregister their analysis plan. A dataset containing only variables required for the proposed analysis is then released to the researchers by a data manager, along with a time- and date-stamped receipt of data access.

References

1 Yung AR, Yung AR, Pan Yuen H, Mcgorry PD, Phillips LJ, Kelly D, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust New Zeal J Psychiatry. 2005 Nov–Dec;39(11–12):964–71.

2 Linscott RJ, Van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med. 2013 Jun;43:1133–49.

3 Van Os J, Linscott RJ. Introduction: the extended psychosis phenotype – relationship with schizophrenia and with ultrahigh risk status for psychosis. Schizophr Bull. 2012 Mar;38(2):227–30.

4 Van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry. 2016 Jun;15(2):118–24.

5 Baumeister D, Sedgwick O, Howes O, Peters E. Auditory verbal hallucinations and continuum models of psychosis: a systematic review of the healthy voice-hearer literature. Clin Psychol Rev. 2017;51:125–41.

6 van der Steen Y, Gimpel-Drees J, Lataster T, Viechtbauer W, Simons CJP, Lardinois M, et al. Clinical high risk for psychosis: the association between momentary stress, affective and psychotic symptoms. Acta Psychiatr Scand. 2017 Jul;136(1):63–73.

7 Reininghaus U, Kempton MJ, Valmaggia L, Craig TKJ, Garety P, Onyejiaka A, et al. Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: an experience sampling study. Schizophr Bull. 2016 May;42(3):712–22.

8 van der Gaag M, van den Berg D, Ising H. CBT in the prevention of psychosis and other severe mental disorders in patients with an at risk mental state: a review and proposed next steps. Schizophr Res. 2019 Jan;203:88–93.

9 Mei C, van der Gaag M, Nelson B, Smit F, Yuen HP, Berger M, et al. Preventive interventions for individuals at ultra high risk for psychosis: an updated and extended meta-analysis. Clin Psychol Rev. 2021 Jun;86:102005.

10 Hayes SC, Strosahl K, Wilson KG. Acceptance and commitment therapy: an experiential approach to behavior change. New York: Guilford Press; 1999.

11 Gaudiano BA, Herbert JD. Acute treatment of inpatients with psychotic symptoms using acceptance and commitment therapy: pilot results. Behav Res Ther. 2006 Mar;44(3):415–37.

12 Johns LC, Oliver JE, Khondoker M, Byrne M, Jolley S, Wykes T, et al. The feasibility and acceptability of a brief acceptance and commitment therapy (ACT) group intervention for people with psychosis: the "ACT for life" study. J Behav Ther Exp Psychiatry. 2016 Mar;50:257–63.

13 Yıldız E. The effects of acceptance and commitment therapy in psychosis treatment: a systematic review of randomized controlled trials. Perspect Psychiatr Care. 2020 Jan;56(1):149–67.

14 Jansen JE, Gleeson J, Bendall S, Rice S, Alvarez-Jimenez M. Acceptance- and mindfulness-based interventions for persons with psychosis: a systematic review and meta-analysis. Schizophr Res. 2020 Jan;215:25–37.

15 Vaessen T, Steinhart H, Batink T, Klippel A, Van Nierop M, Reininghaus U, et al. ACT in daily life in early psychosis: an ecological momentary intervention approach. Psychosis. 2019;11(2):93–104.

16 Myin-Germeys I, Klippel A, Steinhart H, Reininghaus U. Ecological momentary interventions in psychiatry. Curr Opin Psychiatry. 2016 Jul;29(4):258–63.

17 Reininghaus U, Depp CA, Myin-Germeys I. Ecological interventionist causal models in psychosis: targeting psychological mechanisms in daily life. Schizophr Bull. 2016 Mar;42(2):264–9.

18 Batink T, Bakker J, Vaessen T, Kasanova Z, Collip D, van Os J, et al. Acceptance and commitment therapy in daily life training: a feasibility study of an mHealth intervention. JMIR Mhealth Uhealth. 2016 Sep;4(3):e103.

19 van Aubel E, Bakker JM, Batink T, Michielse S, Goossens L, Lange I, et al. Blended care in the treatment of subthreshold symptoms of depression and psychosis in emerging adults: a randomised controlled trial of acceptance and commitment therapy in daily-life (ACT-DL). Behav Res Ther. 2020 May;128:103592.

20 Reininghaus U, Klippel A, Steinhart H, Vaessen T, van Nierop M, Viechtbauer W, et al. Efficacy of acceptance and commitment therapy in daily life (ACT-DL) in early psychosis: study protocol for a multi-centre randomized controlled trial. Trials. 2019 Dec;20(769):1–12.

21 van Aubel E, Vaessen T, Steinhart H, Klippel A, Batink T, van Winkel R, et al. Acceptance and commitment therapy in daily life (ACT-DL) in early psychosis: findings on treatment adherence and acceptability from the multicenter INTERACT randomized controlled trial. JMIR Prepr. 2021.

22 Singh SP, Cooper JE, Fisher HL, Tarrant CJ, Lloyd T, Banjo J, et al. Determining the chronology and components of psychosis onset: the Nottingham onset schedule (NOS). Schizophr Res. 2005 Dec;80(1):117–30.

23 Sheehan D, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Hergueta T, et al. The mini international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview. J Clin Psychiatry. 1998 [cited 2019 May 8];59(Suppl 20):22–3.

24 Guidi J, Brakemeier EL, Bockting CLH, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological recommendations for trials of psychological interventions. Psychother Psychosom. 2018;87(5):276–84.

25 Bach P, Hayes SC. The use of acceptance and commitment therapy to prevent the rehospitalization of psychotic patients: a randomized controlled trial. J Consult Clin Psychol. 2002 Oct;70(5):1129–39.

26 Bach P. ACT with the seriously mentally ill. In: Hayes SC, Strosahl K, editors. A practical guide to acceptance and commitment therapy. New York: Springer; 2005. p. 185–208.

27 van der Gaag M, Nieman DH, Rietdijk J, Dragt S, Ising HK, Klaassen RMCC, et al. Cognitive behavioral therapy for subjects at ultrahigh risk for developing psychosis: a randomized controlled clinical trial. Schizophr Bull. 2012 Nov;38(6):1180–8.
28 Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry. 1992 Sep;149(9):1148–56.
29 Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. Br J Psychiatry. 1990 Dec;157:853–9.
30 Ventura J, Lukoff D, Nuechterlein KH. Brief Psychiatric Rating Scale (BPRS) expanded version (4.0): scales, anchor points and administration manual. Int J Methods Psychiatr Res. 1993;3:227–44.
31 Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull. 2011 Mar;37(2):300–5.
32 Myin-Germeys I, Oorschot M, Collip D, Lataster J, Delespaul P, van Os J. Experience sampling research in psychopathology: opening the black box of daily life. Psychol Med. 2009 Sep;39:1533–47.
33 Myin-Germeys I, Kasanova Z, Vaessen T, Vachon H, Kirtley O, Viechtbauer W, et al. Experience sampling methodology in mental health research: new insights and technical developments. World Psychiatry. 2018 Jun;17(2):123–32.
34 Wilson RS, Shryane N, Yung AR, Morrison AP. Distress related to psychotic symptoms in individuals at high risk of psychosis. Schizophr Res. 2020 Jan;215:66–73.
35 Zipfel S, Junne F, Giel KE. Measuring success in psychotherapy trials: the challenge of choosing the adequate control condition. Psychother Psychosom. 2020;89(4):195–9.
36 Wood L, Williams C, Billings J, Johnson S. A systematic review and meta-analysis of cognitive behavioural informed psychological interventions for psychiatric inpatients with psychosis. Schizophr Res. 2020 Aug;222:133–44.
37 Sitko K, Bewick BM, Owens D, Masterson C. Meta-analysis and meta-regression of cognitive behavioural therapy for psychosis (CBTp) across time: the effectiveness of CBTp has improved for delusions. Schizophr Bull Open. 2020;1(1):sgaa023.
38 Devoe DJ, Farris MS, Townes P, Addington J. Attenuated psychotic symptom interventions in youth at risk of psychosis: a systematic review and meta-analysis. Early Interv Psychiatry. 2019 Feb;13:3–17.
39 Devoe DJ, Braun A, Seredynski T, Addington J. Negative symptoms and functioning in youth at risk of psychosis: a systematic review and meta-analysis. Harv Rev Psychiatry. 2020;28(6):341–55.
40 Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat. 2020 Feb;16:519–34.
41 Veerman SRT, Schulte PFJ, de Haan L. Treatment for negative symptoms in schizophrenia: a comprehensive review. Drugs. 2017 Sep;77(13):1423–59.
42 Peters E, Crombie T, Agbedjro D, Johns LC, Stahl D, Greenwood K, et al. The long-term effectiveness of cognitive behavior therapy for psychosis within a routine psychological therapies service. Front Psychol. 2015 Oct;6:1658.
43 Kramer I, Simons CJP, Hartmann JA, Menne-Lothmann C, Viechtbauer W, Peeters F, et al. A therapeutic application of the experience sampling method in the treatment of depression: a randomized controlled trial. World Psychiatry. 2014 Feb;13(1):68–77.
44 Cosci F. Clinimetric perspectives in clinical psychology and psychiatry. Psychother Psychosom. 2021;90(4):217–21.