Running title: CBCM in UHR

Opening the Black Box of Cognitive-Behavioural Case Management in Ultra-High Risk for Psychosis Clients

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Abstract

Background. Cognitive Behavioural Therapy (CBT) is the first-choice treatment in the ultra-high risk (UHR) for psychosis group. However, CBT is an umbrella term for a plethora of different strategies, and little is known about the dosing or content of CBT and symptomatic outcome. The current study aims to characterise a cognitive-behavioural case management (CBCM) regimen in UHR. Specifically, we examine the association between session dosing, CBCM content and the course of depressive (DS) and attenuated psychotic symptomatology (APS).

Methods. A sample of 242 UHR participants received 6 months of CBCM in the context of the multi-centre Neurapro trial with monthly assessments of symptomatology. Using multilevel regressions, the association between CBCM dose, content and symptomatology over four months follow-up (M1-M4) were investigated.

Results. In M1, higher session dose and symptom assessment predicted increased APS but decreased DS. In M3, higher session dose predicted a decrease in APS. More focus on positive symptoms and symptom assessment predicted decreased DS, while more focus on stress management and negative symptoms predicted increased DS overall.

Conclusion Our findings indicate that the association between dose/content of CBCM and level of symptomatology in a sample of UHR participants depends on time in treatment and varies for DS and APS. CBCM may positively impact depressive symptoms in the beginning of treatment, while APS may be positively impacted only later in the course of treatment. Therefore, it seems important to keep UHR young people engaged in treatment beyond this initial period.

Introduction

The at-risk-mental state or ultra-high risk (UHR) state describes individuals identified as being at enhanced risk of developing a first episode of psychosis, based on the presence of attenuated/short lived psychotic symptoms or a significant drop in functioning in the context of a family history of psychosis. Since the introduction of the UHR criteria[1], considerable research attention has been directed towards the development of effective interventions to positively impact on the trajectory of the UHR state. Growing evidence suggests that psychological therapies such as cognitive-behavioural therapy (CBT) may provide a safe and effective pre-emptive treatment option in UHR clients [2-7]. While recent studies suggest that both psychological and pharmacological interventions reduce rates of transition to psychosis, CBT is, given the favourable risk benefit ratio, considered first choice treatment in UHR groups [8, 9].

CBT-informed therapy is an umbrella term for a plethora of different strategies that has primarily been evaluated as an overall 'treatment package'[10] which, in clinical implementation, is carried out in a variety of forms[11, 12]. CBT comprises various components such as psychoeducation, case formulation, cognitive challenging, or behavioural strategies. Little is known, especially in the field of at-risk mental states, about which components of CBT are in fact delivered and if there are specific CBT 'ingredients' which may be more beneficial than others[10, 13]. Furthermore, the effects of frequency or dosing of CBT (i.e., number of sessions delivered) on treatment outcome has only been partially investigated[4]. The United Kingdom-based EDIE-2 trial showed that a higher number of sessions was associated with less attenuated psychotic symptoms at 12-month follow up [4]. Secondary analyses based on this trial evaluated the presence of certain components in cognitive therapy from file notes and identified a greater treatment effect if case formulation and homework were part of the therapy [13]. Another study in clients with psychosis suggested that CBT was only beneficial for those who received the full nine months of CBT. CBT exclusively consisting of engagement or assessment was not effective, and the therapy appeared to have a detrimental effect on those who did not finish the intervention [10].

Although there is evidence for an early (first four weeks) rapid response to CBT for depression [14, 15], little is known regarding the role of time in treatment in the UHR population. A qualitative study in psychosis investigating clients' experiences of case formulation in CBT suggested that the reaction may be subject to change over time: some clients experienced it initially as confrontational, however this improved over time in most clients [16].

The current study addresses the need to identify effective components of CBT-informed therapy in UHR clients. This may help to develop more targeted and more effective treatment packages for future studies and clinical implementation.

In the present study, a UHR treatment regimen consisting of CBT delivered within a therapeutic case management framework (CBCM) was evaluated. In CBCM, the case manager is a central clinician who both manages general aspects of the patient's care and provides psychotherapy.

The aims of the present study were to (1) characterise the CBCM provided in this study and (2) investigate if dosing of CBCM and/or specific CBCM components received predicted the level of attenuated psychotic symptoms (APS) and depressive symptoms at follow-up assessments.

Based on existing literature, it was hypothesised that a greater number of sessions would be associated with lower levels of symptomatology at follow-up assessments. Exploratory analyses regarding the specific CBCM components and time into treatment were also conducted.

Method

Study design and setting

This study is based on data from the Neurapro trial, a multi-centre randomized controlled trial investigating the effects of omega-3 polyunsaturated fatty acids (PUFA) versus placebo in UHR individuals (ACTRN 12608000475347)[14, 15]. Overall, 304 participants aged 13-40 years and meeting criteria for UHR status received either omega-3 PUFA together with CBCM, or placebo with CBCM. The total study period was 12 months. All participants provided written informed consent prior to enrolment to the study. Details on study methodology and RCT results have been described in detail previously[14, 15]. No significant differences in demographic characteristics, clinical, functional outcomes or CBCM were observed between the experimental and control groups[15], therefore CBCM across both groups was used for analysis in the current study.

Cognitive-Behavioural Case Management

All participants received CBCM adapted to the participant's level of need and symptom profile within the first six months (M0 [baseline] to M6) of study enrolment (longer if indicated), with monthly research visits assessing symptomatic outcome. All clinicians were trained according to a study-specific CBCM manual prior to study start. The manual consist of the following modules: (1) stress management, (2) positive symptoms, (3) negative symptoms, (4) basic symptoms, (5) comorbidity. Session dates and CBCM content were recorded using a checklist completed by the clinician after every CBCM session. The checklist was divided into 13 CBCM components (see Table 1, first column) and an open field was provided for additional written information describing the content of the

session. The content of this open field was reviewed by two authors (JAH and BN) and consensus was reached as to component categorisation.

Since participants received on average less than one CBCM session in M5 and M6, and 80% of the sessions within the 6-month CBCM period occurred during the first four months, the current investigation focused on these first four months (M0-M4) of CBCM.

Session information was assigned to one of four follow-up intervals based on the date of each session, separately for each individual. Sessions occurring between assessments M0 and M1, M1 and M2, M2 and M3, M3 and M4 were assigned to interval 1, 2, 3 and 4, respectively (see Figure 1 for an overview). The following variables were created per individual per interval: Number of sessions received (0, 1, 2, 3, 4 or more) and number of times each specific component was received.

Outcome Measures

Level of attenuated psychotic symptoms (APS) was operationalised using the procedure described in Morrison et al.[4]: Using the Comprehensive Assessment of At-Risk Mental States (CAARMS[16]), we summed the scores of the product of global rating scale score (0-6) and frequency (0-6) of the four subscales unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganised speech. Severity of depressive symptoms was assessed using the Montgomery-Asberg Depression Scale (MADRS[17]).

Statistical Analyses

Due to the hierarchical structure of the data (repeated measures (level 1) nested within participants (level 2), and participants nested within study sites (level 3)), analysis were conducted using the procedure 'mixed' for STATA 14.0 for linear mixed models, bootstrapped with 500 replications.

We conducted a sensitivity analysis including completers only (i.e., participants who completed all symptom assessments). Furthermore, as putting a lagged response variable into a mixed model may yield biased results due to the correlation of the lagged variable with the combined error term ('incidental parameter problem'), we replicated the initial analysis (number of sessions, see below) using the recently formulated STATA command 'xtdpdml', which addresses this problem using maximum likelihood estimation with structural equation modelling (as described by Allison and colleagues[18]).

<u>Number of sessions</u>

To investigate the association between number of sessions received and level of severity of APS, we applied the procedure of autoregressive lagged modelling as described in Zilcha-Mano et al[19].

Number of sessions was regressed on APS, while controlling for previous symptomatic levels (APS $_{(T-1)}$, see Figure 1.) Additionally, we controlled for MADRS scores (depressive symptoms), gender, age, number of sessions already received and number of days within that interval. As the association between number of sessions received and APS may depend on time in treatment, an interaction term between number of sessions (continuous) and assessment time point (categorical, M1-M4) was introduced [19]. Interaction terms were removed when not significant. For depressive symptoms, number of sessions were regressed on MADRS scores, while controlling for previous MADRS score $_{(T-1)}$ and APS (remainder as for APS model).

CBCM components

The same model as described above was applied to investigate the association between specific CBCM components (number of times each component received) and symptomatic levels (APS and MADRS scores).

Components that may be related to outcome were initially identified in a lagged regression model unadjusted for the other components. Components which constituted more than 15% of the sessions (see Table 1) and with significant associations were included in the full model, which was adjusted for all other components. For APS as outcome, full model components included case management, monitoring, assessment of symptoms, stress management, positive symptoms, and homework. For MADRS as outcome, full model components included monitoring, assessment of symptoms, stress management, positive symptoms, negative symptoms, basic symptoms and homework. As the association between CBCM component and APS/MADRS may depend on time in treatment, an interaction term between component and time point (M1-M4) was introduced [19]. Interaction terms were removed when not significant. We used the same autoregressive lagged modelling structure: we controlled for previous symptoms, while adjusting for gender, age, number of sessions received and number of days within each interval. As not all CBCM components were received by all participants, each model only included those participants who received the component at least once.

As this study aimed to identify effective intervention elements, participants who transitioned to first-episode psychosis during follow-up were excluded from analyses.

Results

Of the 304 participants randomized in the parent study[15], 268 participants (88%) had at least one symptom assessment other than baseline with CBCM checklist data on at least one session available.

Twenty-six participants (9%) were excluded because they transitioned to a full psychotic episode during follow-up. Thus, a total of 242 participants (80%) were included in analyses.

Table 2 displays baseline demographic and clinical information. Participants received on average a total of 10.4 sessions (SD 5.83, Range 1-32). The number of sessions per month significantly decreased over time (p<.001). The most prevalent CBCM components administered were monitoring, stress management and assessment of symptoms (Table 1). The proportion of the components general information/psychoeducation, monitoring, assessment of symptoms, positive symptoms, basic symptoms, and homework decreased over time (p<.01). The proportion of relapse prevention and termination increased with time (p<.001). All other components remained stable.

Number of sessions and symptomatic outcome

In predicting the level of APS, the overall interaction between number of sessions and assessment time point was significant ($\chi^2(3) = 19.61$, p<.001). Using Stata's procedure MARGINS, the slopes per time point were subsequently estimated. For M1, there was a significant positive association between number of sessions and level of APS (i.e., more sessions significantly predicted higher level of APS at the end of M1: b = 2.01, SE = .67, p = .003, 95% CI [.69,3.33]; Figure 2) while by M3, a significant negative association between number of sessions and the level of APS was observed (i.e., more sessions significantly predicted a lower level of APS: b = -1.29, SE = .45, p=.004, 95% CI [-2.17,-.41]; Figure 2). Sensitivity analyses using completers only (n=188) and the xtdpdml procedure yielded similar results: a positive association between number of sessions and APS in M1, and a negative association for M2-M4 (see S1).

In predicting the MADRS scores, there was an overall interaction between number of sessions and time point ($\chi^2(3) = 12.59$, p = .006). Using Stata's procedure MARGINS, the slopes per time point were subsequently estimated. There was a significant negative association between number of sessions and MADRS at M1 (i.e., more sessions significantly predicted lower levels of depressive symptoms at the end of M1: b=-.89, SE=.34, p=.009). However, no significant association was observed for the other months (p values between .123 and .965). Sensitivity analyses including completers only and the xtdpdml procedure yielded a similar pattern: a negative association between number of sessions and depressive symptoms in M1, and no association in M2-M4 (see S1).

CBCM Components and symptomatic outcome

Family work, crisis management, and relapse prevention/termination were *a priori* excluded from analyses because these components constituted less than 15% of the CBCM sessions (see Table 1).

Table 3 provides the results of the full models. For APS levels, most components showed an interaction with time, with a similar pattern to that seen for number of sessions. There was a positive association between the CBCM component assessment of symptoms and level of APS during the first month. For the components case management, monitoring, and stress management, a negative association was observed from M2 or M3, which approaches significance in M3.

For the MADRS scores, the components did not yield an interaction with time, but a negative main effect for the components assessment of symptoms and positive symptoms (i.e. more assessment of symptoms/focus on positive symptoms predicted less depressive symptoms overall), and a positive main effect for stress management and negative symptoms were observed.

Discussion

Our study investigated the content and dosing of a CBCM regimen in UHR participants provided in the context of the Neurapro trial, both descriptively as well as in association with level of depressive and attenuated psychotic symptomatology. Our findings indicate that the majority of CBCM occurred within the first four months of the protocol and there was substantial variation in the number of sessions received (ranging from 1 to 32 sessions), likely reflecting variation in clients' level of engagement with the psychosocial aspect of intervention provided during the trial. The most frequently delivered elements of CBCM were monitoring, stress management and assessment of symptoms.

In this study, we found that a greater number of sessions predicted an increased level of APS at the end of the first four weeks of treatment, an association which was reversed by M3 (i.e. more sessions was associated with a decrease in APS). To our knowledge, our findings are the first to indicate that the association between 'dosing' of CBCM (i.e., number of sessions received) and level of APS may depend on time in treatment. These results appear to be robust as the same pattern was observed when two separate sensitivity approaches were applied.

These novel findings may be interpreted in several ways. First of all, it is possible that the early, 'unfavourable' CBCM-APS association is related to a form of response bias. At the beginning of the treatment, the amount of psychoeducation regarding UHR is high, potentially leading to a change in how and what experiences are revealed compared to the initial assessment. In other words, participants may be better informed, better able to describe, and potentially reveal new experiences they did not at the initial assessment, leading to a higher rating of APS on the CAARMS for those who received more CBCM sessions. Alternatively, the positive association between number of sessions and level of APS in the first four weeks may be driven by participants with increasing APS receiving more sessions, i.e., an increase in clinical contact in response to worsening symptoms. Similarly, the negative association between number of sessions and APS in M3 may be driven by participants with decreasing APS receiving less sessions. However, the probability of this form of reverse causation has been reduced by controlling for the previous level of APS for every participant.

Conversely, and speculatively, it may be the case that at the very outset of treatment, CBCM leads to an initial intensification of APS. In support of this, Dunn et al.[10] identified a potential negative effect of CBT in patients with psychosis who stopped the treatment prematurely. Furthermore, a qualitative study on clients' experience of CBT's case formulation suggested a change over time with some clients experiencing it as confrontational in the beginning, but with an improvement of those feelings over time in most clients[20]. Another qualitative study investigating the subjective experiences of UHR participants of the EDIE-2 trial indicated that many clients disclosed their

unusual psychological experiences for the first time in their lives[21]. Clients also suggested that talking about these experiences was challenging or difficult[20, 21]. It is conceivable that initial confrontation with these unusual experiences at the beginning of CBCM treatment is responsible for the initial increase in reported APS. This is speculative and our results need to be replicated before firm conclusions can be drawn. It may reflect some traditional views of psychotherapy for psychosis[10, 22]: Talking about the content of psychotic experiences was sometimes discouraged from this perspective as it could lead to an aggravation or 'inadvertent collusion'[23]. Most importantly, however, our results suggest that participants may start to benefit from more sessions of CBCM when they continue treatment.

A change in therapeutic alliance may also play a role in the observed association between CBCM dosing and APS. Therapeutic alliance is defined as the quality of the relationship between client and therapist and is regarded to play a pivotal role in the outcome of psychotherapy[24]. In a sample of people with acute first- or second-episode psychosis, Goldsmith et al.[22] showed that CBT may have detrimental effects (i.e. worse symptomatic outcome) when the therapeutic alliance is poor, and positive effects when the alliance is good. More importantly, improving the therapeutic alliance was associated with enhanced outcome[22]. In the current study, the changing association between CBCM dosing and APS may be a result of an improving therapeutic alliance over time.

For the CBCM components, we observed a similar pattern as for the dosing: when a specific component predicted decreased APS, this occurred in M3 (however, associations began to change from positive to negative in M2); and if a specific component predicted increased symptoms, this occurred in the first four weeks. Assessment of symptoms was positively associated with level of reported APS at the end of M1. This is in line with the previous speculations on (1) disclosing APS for the first time, (2) becoming more knowledgeable about APS symptoms. It is consistent with a study by Dunn et al. in patients with psychosis which indicated that CBT merely consisting of assessment and engagement was not beneficial[10] and the well-known phenomenon of psychotic clients being guarded about their symptoms early on[25].

The association between CBCM and depressive symptomatology seemed to follow a different pattern than for APS. In the case of depression, a higher number of sessions predicted less depressive symptoms in the first four weeks, after which no association between dosing of CBCM and level of depressive symptoms was observed. This finding is in line with the well-known and long-established 'early rapid response' to CBT in depression[26-28], which has demonstrated that most change occurs in the first four weeks of CBT, after which time the response flattens. It has been argued that this response is due to nonspecific factors such as an amelioration of the hopelessness factor of depression at the beginning of treatment, rather than CBT-specific factors such as cognitive

restructuring or behavioural activation[27]. Alternatively, the association between CBT and depressive symptoms in the first four weeks may be driven by participants with decreasing depressive symptoms receiving less sessions because they are already responding, although the plausibility of this explanation is reduced in the current analysis by our statistical approach (please see above).

Regarding the specific components, results showed an interesting contrast to APS. The assessment of symptoms component predicted less depressive symptoms. In contrast to APS, reporting symptoms may be associated with a form of relief as reflected in less depressive symptoms, especially at the start of the treatment. A similar interpretation is conceivable for the finding that a focus on positive symptoms predicted less depressive symptoms. In other words, disclosing and working on one's attenuated psychotic experiences may not be associated with a decrease in intensity or frequency of those experiences, but with a decreased overall affective response.

Unexpectedly, stress management and negative symptoms seemed to predict overall more depressive symptoms. A number of different explanations of this finding are possible. First, in contrast to level of APS, which showed a negative association with stress management in M3 (i.e., more stress management, less APS), the management of stress consisting mainly of stress management techniques may simply not be beneficial for addressing depressive symptoms in this group. Secondly, the observed positive association between stress management/negative symptoms and depressive symptoms may reflect increasing depressive symptoms: the clinician may respond by engaging more in stress management techniques.

Limitations

As this study was a secondary analysis of the Neurapro trial and was not specifically designed to evaluate CBCM, it comes with the clear limitations of no control group (i.e., a group who received no CBCM or a different form of psychotherapy). Furthermore, components were not randomly assigned, but selected on the basis of participant presentation. Although the current analytical approach reduced the possibility of reverse causation, we cannot ascertain cause and effect. That is, symptomatic levels may be impacted by CBCM, CBCM may be impacted by participant presentation, or both. Furthermore, it is likely that the different components may interact in impacting on symptomatic levels and there may be order effects of the specific CBCM components. Moreover, we were not able to investigate certain components (i.e., crisis management, family intervention) as these elements were delivered infrequently. However, our exploratory study can be used to generate hypotheses to be experimentally tested in the future. In light of psychotherapeutic interventions being a preferred option to medication in young people at risk of psychotic disorder, it

is important to identify the active ingredients or key components of CBT-informed therapies. Recommendations for future studies are dismantling studies or trials randomising participants to components. Furthermore, it is important to measure therapeutic alliance over the course of CBT intervention and capture the detailed subjective experience of the participants. Understanding the specific structure (e.g., duration) and content (components) of CBT that is most effective for symptoms in this patient group can critically inform future treatment.

Conclusion

Our findings indicate that the association between dose/content of CBCM and level of symptomatology in a sample of UHR participants depends on time in treatment and varies for depressive symptoms and APS. CBCM may positively impact depressive symptoms in the beginning of treatment, while APS may be positively impacted only later in the course of treatment, after an initial refractory phase. Therefore, it may be important to keep UHR young people engaged in treatment beyond this initial period and to increase awareness and validation of the potentially confronting and destabilising aspect of talking and discussing APS often for the first time. Future studies that randomise participants to CBCM or CBT components are needed to replicate the current findings and ascertain cause and effect.

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Table 1. Components of cognitive-behavioural case management

Components	% of sessions
Included in analysis	
Monitoring	68.4
Stress Management	51.3
Assessment of symptoms	48.2
Comorbidity	39.4
Negative symptoms	38.8
Homework	37.6
Positive symptoms	30.3
Case Management	21.7
General Information/Psychoeducation	21.3
Basic Symptoms	17.3
Not included in analysis [a]	
Crisis Management	14.4
Family Work	14.4
Relapse Prevention and Termination	10.9

[a] Excluded as these elements constituted less than 15% of the sessions

Table 2.Baseline demographic and clinical data (N=242)

Characteristic		Mean (SD, Range) or N (%)
	Age	18.9 (4.41, 13-37)
Gender	Female	130 (54%)
	Male	112 (46%)
Ethnicity	Caucasian	197 (81%)
	Black or African American	7 (3%)
	Asian	31 (13%)
	Other	7 (3 %)
Education	Primary school	90 (37%)
	Secondary school, discontinued	45 (19%)
	Secondary school, completed	66 (27%)
	Trade or technical training	26 (11%)
	Undergraduate university course	14 (6%)
	Missing	1 (0%)
	APS	36.9 (17.04, 0-96)
	MADRS	19.1 (8.87, 0-39)

Table 3. Results for the mixed model investigating the association between cognitive-behavioural case management component and level of attenuated positive symptom/level of depressive symptoms

Component	Test statistic	Adjusted Estimate (SE) [95% CI] for APS/MADRS per month
APS		
Case Management x time (N=128)	$\chi^2(3) = 8.17$, **p = .043**	M1: b = 1.87 (1.06) [-.22,3.96] M2: b = -1.59 (1.08)[-3.7,.54] **M3: b = -1.68 (.88)[-3.40,.05]^T** M4: b = -2.01 (1.37)[-4.69,.67]
Monitoring x time (N=211)	$\chi^2(3) = 19.23$, **p <.001**	M1: b = 1.35 (.78) [-1.77,2.89] M2: b = -1.21 (.70) [-2.59, .17] **M3: b = -1.27 (.66) [-2.56,.02]^T** M4: b = -.61 (.86) [-2.29,1.07]
Assessment x time (N=193)	$\chi^2(3) = 14.65$, **p = .002**	**M1: b = 1.56 (.68) [.24,2.88]*** M2: b = -.84 (.84) [-2.49,.80] M3: b = -1.31 (.86) [-3.00,.38] M4: b = -.79 (.86) [-2.48-.91]
Stress Management x time (N=209)	$\chi^2(3) = 9.23$, **p = .026**	M1: b = .93(.71) [-.46,2.32] M2: b = -1.34 (.80) [-2.91,.24] **M3: b = -1.41 (.73) [-2.85, 0.22]^T** M4: b =-.50 (.84) [-2.15,1.15]
Positive symptoms (N=156)	b = 1.14 (.64) [-.13,2.40]	N/A
Homework (N=161)	b= .31 (.66) [-.98,1.61]	N/A
MADRS		
Monitoring (N=211)	b = .28(.31) [-.34,.90]	N/A
Assessment of symptoms (N=193)	**b = -.92 (.3 6) [-1.62,-.21]****	N/A
Stress Management (N=209)	**b = .66 (.27) [.13,1.19]***	N/A
Positive Symptoms (N=156)	**b =-.97 (.34) [-1.63,-.30]****	N/A
Negative Symptoms (N=174)	**b = 1.13 (.28) [.58,1.69]*****	N/A
Basic Symptoms (N=103)	b = -.24 (.46) [-1.14,.67]	
Homework (N=161)	b = .36 (.28) [-.18,.91]	N/A

***=p<.001; **=p<.01; *=p<.05; T=p<.057

CBCM, cognitive-behavioural case management; APS, attenuated psychotic symptoms; MADRS=Montgomery-Asberg Depression Scale; M=Month

Figure legends

Figure 1. Overview of the study protocol. CBCM, cognitive-behavioural case management; APS, attenuated psychotic symptoms; MADRS, Montgomery -Asberg Depression Scale.T_0=Baseline, T_1-T_4 = Follow-up assessments

Figure 2. Predicted values for APS for Month 1 and Month 3 for different CBCM dosing. The x-axis shows the number of CBCM sessions. The y-axis is the predictive margins. Statistics in Table 3. CBCM, cognitive-behavioural case management; APS, attenuated psychotic symptoms.