Running title: CBCM in UHR

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

Jessica A. Hartmann[a,b], Patrick D McGorry[a,b], Stefanie J. Schmidt[c], G. Paul Amminger[a,b], Hok Pan Yuen[a,b], Connie Markulev[a,b], Gregor E. Berger[d], Eric Y.H. Chen[e], Lieuwe de Haan[f], Ian B. Hickie[g], Suzie Lavoie[a,b]; Meredith J. McHugh[a,b], Nilufar Mossaheb[h], Dorien H. Nieman[f], Merete Nordentoft[i], Anita Riecher-Rössler[j], Miriam R. Schäfer[a,b], Monika Schlögelhofer[h,k], Stefan Smesny[l], Andrew Thompson[m], Swapna Kamal Verma[n], Alison R. Yung[o], Barnaby Nelson[a,b]

[a]Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Australia

[b]Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia

[c]University Hospital of Psychiatry, University of Bern, Bern, Switzerland

[d]Child and Adolescent Psychiatric Service of the Canton of Zurich, Zurich, Switzerland

[e]Department of Psychiatry, University of Hong Kong, Hong Kong, China

[f]Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

[g]Brain and Mind Research Institute, University of Sydney, Sydney, Australia

[h]Department of Psychiatry and Psychotherapy, Clinical Division of Social Psychiatry, Medical University of Vienna, Vienna, Austria

[i]Psychiatric Centre Bispebjerg, Copenhagen, Denmark

[j]University of Basel Psychiatric Hospital, Basel, Basel, Switzerland

[k]Department of Child and Adolescent Psychiatry, Medical University Vienna, Vienna, Austria

[l]Department of Psychiatry, Jena University Hospital, Jena, Germany

[m]Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick, Coventry, England

[n]Institute of Mental Health, Singapore, Singapore

[o]Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK

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Corresponding author:

Dr Jessica Hartmann, 35 Poplar Road, Parkville VIC 3052

Email: Jessica.hartmann@orygen.org.au

Phone: +61 423 289 849

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 association between intensity and content of CBT and severity of symptomatic outcome.

Methods: A sample of 268 UHR participants received six months of cognitive behavioural therapy with case management (CBCM) in the context of the multi-centre Neurapro trial with monthly assessments of attenuated psychotic symptoms (APS). Using multilevel regressions and controlling for initial severity of APS, the association between (1) number of CBCM sessions received and severity of APS, and (2) specific CBCM components and severity of APS, were investigated.

Results: In Month 1, a higher number of sessions and more assessment of symptoms predicted an increase of APS, while in Month 3, a higher number of sessions and more monitoring predicted a decrease in level of APS. More therapeutic focus on APS predicted an increase of APS overall.

Conclusions: Our findings indicate that the association between intensity/content of CBCM and severity of APS in a sample of UHR participants depends on time in treatment. CBCM may positively impact severity of APS later in the course of treatment. Therefore, it would seem important to keep UHR young people engaged in treatment beyond this initial period. Regarding the specific content of CBCM, a therapeutic focus on APS may not necessarily be beneficial in reducing the severity of APS, a possibility in need of further investigation.

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 intensity 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 intensity of CBCM and/or specific CBCM components received predicted the severity of subsequent attenuated psychotic symptoms (APS).

Based on existing literature, it was hypothesised that a greater number of sessions would be associated with lower levels of subsequent symptomatology. 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, double-blind 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]. The study was presented to participants as a study of the effects of a nutritional supplement (omega 3 fatty acids) in addition to a psychosocial intervention (CBCM). In other words, the psychological intervention was presented as and viewed by participants as integral to the intervention package. No significant differences in any demographic characteristics, clinical, functional outcomes or CBCM variables were observed between the experimental and control groups at baseline or 12 month follow-up [15]. No significant differences in any of these variables were observed at medium term (3.5 years; manuscript in preparation). Therefore, CBCM across both groups was used for joint analysis in the current study.

Cognitive-Behavioural Case Management (CBCM)

CBCM consists of CBT within a case management framework and is globally implemented in numerous UHR clinics (for details, please see the PACE Clinic Manual: A Treatment Approach for

Young People at Ultra High Risk for Psychosis [16]). All clinicians were extensively trained by senior psychologists according to a study-specific CBCM manual prior to study start. The manual consists of the following modules: (1) stress management, (2) positive symptoms, (3) negative symptoms, (4) basic symptoms, (5) comorbidity. In order to ensure treatment fidelity, regular (fortnightly) individual and group supervision was maintained. At the different sites, there was local supervision with a senior clinician as well as regular supervision with senior psychologists at the leading site (Orygen) via Skype. Sessions were audiotaped with client consent. 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).

Procedure

All participants received CBCM adapted to the participant's level of need and symptom profile within the first six months of study enrolment. Symptomatic outcome was assessed at the end of each month. Since participants received on average less than one CBCM session in Month 5 and Month 6, 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 (Month 0-Month 4) of CBCM.

The following variables were created per individual: Number of sessions received (0, 1, 2, 3, 4 or more) and number of times each specific component was received.

Outcome Measures

Severity of attenuated psychotic symptoms (APS) was operationalised as described in Morrison et al. [4]: Using the Comprehensive Assessment of At-Risk Mental States (CAARMS [17]), 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.

Statistical methods

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.

Additionally, we conducted a sensitivity analysis including 'completers' only. A completer was defined as a participant who did not drop out, but completed all research interviews.

Number of sessions

To investigate the association between number of sessions received and severity of APS while accounting for prior symptomatic levels, we applied the same procedure as described in Zilcha-Mano et al [19]. Number of sessions during a month was used to predict subsequent severity of $APS_{(T)}$, while controlling for prior severity of APS ($APS_{(T-1)}$). Additionally, we controlled for depressive symptoms, gender, age, and number of sessions already received. As the association between number of sessions and APS may depend on time in treatment, an interaction term between number of sessions and assessment time point (categorical, Month 1-Month 4) was introduced [19]. Interaction terms were removed when not significant.

CBCM components

The same model as described above was applied to investigate the association between specific CBCM components and severity of APS.

Components that may be related to outcome were initially identified in a univariate regression model unadjusted for the other components. Components that significantly predicted APS in the univariate models and components which constituted more than 15% of the sessions (see Table 1) were included in the full, multivariate model, adjusted for the other components. As not all CBCM components were received by all participants, each model included only those participants who received the component at least once.

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. Table 2 displays baseline demographic and clinical information. Participants received on average a total of 10.5 sessions (SD 6.02, 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

In predicting severity of APS, the interaction between number of sessions and assessment time point (Month 1 –Month 4) was significant ($\chi^2(3) = 17.93$, $p<.001$). Using Stata's procedure MARGINS, the

slopes per month were subsequently estimated. For Month 1, there was a significant positive association between number of sessions and severity of APS: more sessions significantly predicted *an increase* of APS (b = 1.61, SE = .59, p = .007, 95% CI [.44,2.78]). By Month 3, a significant negative association between number of sessions and the level of APS was observed: more sessions significantly predicted a *decrease* of APS (b = -1.23, SE = .46, p=.008, 95% CI [-2.14,-.32]). In other words, while accounting for the initial severity of APS, each additional CBCM session attendance was associated with a 1.6 point increase in severity of APS by the end of the first month, while during Month 3, each additional session attended was associated with a 1.2 point reduction of severity of APS. Sensitivity analyses using completers only (n=207) yielded similar results: a positive association between number of sessions and APS in Month 1 (b = 1.67, SE = .69, p = .016, 95% CI [.32,3.02]), and a negative association in Month 3 (b = -1.20, SE = .46, p = .009, 95% CI [-2.10,-.30]).

CBCM Components

'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). The components 'psychoeducation', 'comorbidity', 'negative symptoms', 'homework', and 'basic symptoms' were not included in the full model as they failed to show an association with APS in the univariate models.

Table 3 provides the results of the full, multivariate models. Included were the components 'case management', 'monitoring', 'assessment of symptoms', 'stress management' and 'positive symptoms'. 'Monitoring' and 'assessment of symptoms' showed an interaction with time point, with a similar pattern to that seen for number of sessions. There was a positive association between the component 'assessment of symptoms' and severity of APS during the first month (i.e. more assessment, more symptoms). For the component 'monitoring', a negative association was observed for month 3 (i.e., more monitoring, less symptoms). 'Stress management' and 'case management' did not show a significant association with APS in the full model. The component 'positive symptoms' demonstrated a positive association with APS (i.e. more focus on positive symptoms, more APS) throughout the treatment.

Discussion

Our study investigated the content and intensity of a CBCM regimen in UHR participants provided in the context of the Neurapro trial, both descriptively as well as in association with severity of 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' clinical presentations and varying levels of engagement. 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 a higher level of APS at the end of the first four weeks of treatment, an association which was reversed by Month 3 (i.e. more sessions was associated with lower level of APS). To our knowledge, our findings are the first to indicate that the association between 'intensity' 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 a sensitivity approach was applied including completers only.

These novel findings may be interpreted in several ways. First of all, it is possible that the initial, '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 Month 3 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 is associated with 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 [18]. 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 [19]. Clients also suggested that talking about these experiences was challenging or difficult [18, 19]. It is conceivable that initial confrontation with these unusual experiences at the beginning of CBCM treatment is responsible for the initial unfavourable CBCM-APS association. 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, 20]: Talking about the content of psychotic experiences was sometimes discouraged from this perspective as it could lead to an aggravation or 'inadvertent collusion'[21]. 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 intensity 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 [22]. In a sample of people with acute first- or second-episode psychosis, Goldsmith et al.[20] 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 [20]. In the current study, the changing association between CBCM intensity and APS may be a result of an improving therapeutic alliance over time. Finally, it is also possible that initially, CBT is somewhat difficult for this client group to engage with, possibly due to it being an overly formalised approach that may be challenging for young people, particularly when distressed and being oriented to a new service [2]. This interpretation would suggest that a therapeutic approach that emphasises engagement, 'meeting the person where they are at' and is possibly more supportive and person-centred in nature may be indicated in the very early phases of treatment for this group, before moving onto more concerted or focused CBT techniques.

Regarding the CBCM components, only the components 'monitoring', 'assessment of symptoms', and 'positive symptoms' were significantly associated with severity of APS in the full model. 'Monitoring' and 'assessment' followed the same pattern as number of sessions: In interaction with time, 'assessment of symptoms' was positively associated with APS (i.e. more assessment, higher level of symptoms) during the first month only, while this association changed its direction in month 3 (without reaching significance). 'Monitoring' was negatively associated with APS in month 3 only (i.e. more monitoring, less APS), and an investigation of the coefficients shows that also in this case, the association changed its direction compared to month 1.

The finding regarding the component 'positive symptoms' followed a different pattern. More focus on positive symptoms predicted a higher level of APS across the investigated intervention period (i.e. no interaction with time). Again, this finding can be interpreted in a number of ways. First, while we control for level of APS during the previous assessment, it is still possible that participants demonstrate increasing APS in the few weeks prior to a research assessment. This may be picked up by the clinician, who responds with an increased focus on APS during CBCM sessions. Conversely and

speculatively, focusing on APS may not be beneficial in decreasing its level, in line with what is discussed and reviewed above.

The fact that most other components did not show significant associations with symptomatic outcome may be due to a lack of power, and more research in larger samples is required.

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 (i.e. controlling for previous symptomatic levels) 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.

Our findings, while preliminary, indicate that the association between intensity/content of CBCM and severity of APS in a sample of UHR participants depends on time in treatment. CBCM may positively impact APS only later in the course of treatment, after an initial refractory phase. Therefore, it may be important for clinicians to keep UHR young people engaged in treatment beyond this initial period and to increase awareness and validation of the potentially confronting and destabilising nature of talking about and discussing APS often for the first time. Alternatively, therapeutic approaches that emphasise engagement, possibly more supportive and person-centred in nature, may be indicated in the very early phases of treatment for this group. Furthermore, a therapy focus on positive symptoms may not be beneficial for all clients throughout treatment. In line with the suggestions of Richardson and Doster [23], clinicians need to carefully balance

treatment along three dimensions of baseline risk (i.e. the risk the person would be at without treatment), expected responsiveness to treatment, and possible vulnerabilities (e.g. possible adverse effects) imposed by the treatment [24]. 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=268)

Characteristic		Mean (SD, Range) or N (%)
	Age	18.9 (4.35, 13-37)
Gender	Female	146 (54%)
	Male	122 (46%)
Ethnicity	Caucasian	216 (80%)
	Black or African American	7 (3%)
	Asian	35 (13%)
	Other	10 (4%)
Education	Primary school	105 (39%)
	Secondary school, discontinued	49 (18%)
	Secondary school, completed	71 (27%)
	Trade or technical training	28 (11%)
	Undergraduate university course	14 (5%)
	Missing	1 (0%)
	APS	37.3 (16.89, 0-96)
	MADRS	19.3 (8.92, 0-39)

Table 3. Results for the mixed model investigating the association between cognitive-behavioural case management component and level of attenuated positive symptoms. When interactions with time were not significant, the overall effect was estimated.

Component	Component by time (interaction)	Coefficient (SE) [95% CI] per month (simple slopes)	Coefficient (SE) [95% CI] overall (main effect)
APS			
Case Management (N=140)	$\chi^2(3) = 5.51$	-	b = -.23 (.61) [-1.44,.97]
Monitoring (N=233)	**$\chi^2(3) = 11.06$****	Month 1: b = .36 (.66) [-.94,1.66] Month 2: b = -1.04 (.66) [-2.33, .25] **Month 3: b = -1.55 (.60) [-2.73,-.37]**** Month 4: b = .03 (.83) [-1.58,1.65]	-
Assessment (N=215)	**$\chi^2(3) = 8.01$***	**Month 1: b = 1.49 (.59) [.33,2.65]**** Month 2: b = .27 (.76) [-1.22,1.75] Month 3: b = -.86 (.85) [-2.52,.81] Month 4: b = 1.29 (.96) [-.59,3.16]	-
Stress Management (N=229)	$\chi^2(3) = 5.38$	-	b = -.44 (.45) [-1.32, .44]
Positive symptoms (N=174)	$\chi^2(3) = 2.63$	-	**b = 1.69 (.60) [.51,2.87]****

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

CBCM, cognitive-behavioural case management; APS, attenuated psychotic symptoms