Received: 16 May 2018 | Revised: 27 September 2018 | Accepted: 26 December 2018

DOI: 10.1111/eip.12781

WILEY

ORIGINAL ARTICLE

Multimodal prevention of first psychotic episode through N-acetyl-L-cysteine and integrated preventive psychological intervention in individuals clinically at high risk for psychosis: Protocol of a randomized, placebo-controlled, parallel-group trial

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Funding information
Bundesministerium für Bildung und Forschung, Grant/Award Number: 01EE1407C, 01EE14071

Aim: Meta-analyses indicate positive effects of both antipsychotic and cognitive-behavioural interventions in subjects clinically at high risk (CHR) for psychosis in terms of a delay or prevention of psychotic disorders. However, these effects have been limited regarding social functioning and the relative efficacy of both types of interventions remains unclear. Furthermore, neuroprotective substances seem to be a promising alternative agent in psychosis-prevention as they are associated with few and weak side-effects.

Methods: In this multi-centre randomized controlled trial (RCT), we investigate the effects of two interventions on transition to psychosis and social functioning: (a) an integrated preventive psychological intervention (IPPI) including stress-/symptom-management and social-cognitive remediation; (b) N-acetyl-L-cysteine (NAC) as a pharmacological intervention with glutamatergic, neuroprotective and anti-inflammatory capabilities.

Results: This is a double-blind, placebo-controlled RCT with regard to NAC and a single-blind RCT with regard to IPPI using a 2 × 2-factorial design to investigate the individual and combined preventive effects of both interventions. To this aim, a total of 200 CHR subjects will be randomized stratified by site to one of four conditions: (a) IPPI and NAC; (b) IPPI and Placebo; (c) NAC and psychological stress management; (d) Placebo and psychological stress management. Interventions are delivered over 26 weeks with a follow-up period of 12 months.

Conclusion: This paper reports on the rationale and protocol of an indicated prevention trial to detect the most effective and tolerable interventions with regard to transition to psychosis as well as improvements in social functioning, and to evaluate the synergistic effects of these interventions.

KEYWORDS

clinical high risk, cognitive remediation, N-acetyl-L-cysteine, prevention, psychosis, social cognition

1 | INTRODUCTION

Psychotic disorders are associated with huge individual and societal burden. Therefore, they are among the most expensive brain-related disorders in Europe (Vigo, Thornicroft, & Atun, 2016; Wittchen et al., 2011). To fight these detrimental outcomes, indicated prevention approaches have been developed to target individuals at clinical high risk (CHR) for psychosis (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015).

1.1 | Need for integrated preventive psychological interventions

Most studies have focused on reducing risk-symptoms by improving symptom management and found significantly larger effects on transition rates than control conditions (Schmidt et al., 2015; Van der Gaag et al., 2013). However, social functioning is an important but neglected outcome given that substantial functional impairments are already present in CHR subjects, often worsen until transition to psychosis and are even predictive of it (Addington et al., 2017; Fusar-Poli et al., 2015; Ruhrmann et al., 2010; Velthorst et al., 2018). Current approaches did not produce significantly larger effects on social functioning than control conditions (Schmidt et al., 2015; Van der Gaag et al., 2013). Thus, novel interventions are needed to directly target factors modulating social functioning, such as social cognition (Cotter et al., 2017; Glenthøj et al., 2016; Schmidt, Mueller, & Roder, 2011). Social cognition as the mental operations underlying social interactions comprises the following domains: social and emotional perception, Theory of Mind and social attribution styles (Green et al., 2008; Pinkham, Penn, Green, & Harvey, 2015). These domains are already impaired in CHR subjects (Lee et al., 2015; Van Donkersgoed, Wunderink, Nieboer, Aleman, & Pijnenborg, 2015). Although the need of social-cognitive remediation for CHR subjects has been highlighted in recent reviews (Glenthøj, Hjorthøj, Kristensen, Davidson, & Nordentoft, 2017; Statucka & Walder, 2013), there is still a lack of such evaluation studies.

Moreover, current prevention approaches often neglect that, in addition to the increased risk for developing psychosis, CHR individuals already suffer from multiple mental problems, such as distress and poor coping skills (Schmidt, Grunert, Schimmelmann, Schultze-Lutter, & Michel, 2014). Therefore, in line with stress-vulnerability models (Gispen-de Wied & Jansen, 2002; Nuechterlein & Dawson, 1984), interventions to improve stress management should also be part of psychosis prevention programs.

1.2 | Need for novel neuroprotective interventions

Preventive interventions require a most favourable risk-benefit ratio. However, antipsychotics used in most pharmacological trials showed unfavourable side-effects (Ruhrmann et al., 2012). Therefore, potential neuroprotective substances with only few and weak side-effects seem promising. One such neuroprotective agent is N-acetyl-L-cysteine (NAC), which targets dysfunctional glutamatergic neurotransmission, shown to be altered in CHR subjects (Treen et al., 2016). NAC can elevate brain glutathione (GSH), a major cellular redox regulator and anti-oxidant protecting cells from the damages of reactive oxygen species (Meister & Anderson, 1983). Brain GSH levels have shown to be decreased in the medial prefrontal cortex, in the caudate region and cerebrospinal fluid of drug-naive patients with schizophrenia (Do et al., 2000; Yao, Leonard, & Reddy, 2006). GSH deficiency aggravates neuronal oxidative stress linked to abnormal metabolism of dopamine and glutamate in schizophrenia (Castagné, Rougemont, Cuenod, & Do, 2004; Smythies, 1997). Polymorphisms of genes involved in GSH synthesis, leading to suppressed protein expression and reduced GSH levels, have also been associated with an enhanced risk for schizophrenia (Gysin et al., 2007; Tosic et al., 2006). NAC increases plasma cysteine levels, thus filling up depleted GSH levels and preventing GSH depletion (Kamboj, Kiran, & Sandhir, 2006). In support of this, NAC has been shown to be superior to placebo in trials in patients with schizophrenia (Berk et al., 2008; Lavoie et al., 2007; Rapado-Castro et al., 2017; Retsa et al., 2018). The fact that the mechanisms of action of NAC overlap with the GSH-linked pathophysiology of schizophrenia and CHR states as well as its benign tolerability and safety profile bear the promise to prevent transition to psychosis by augmenting neuronal GSH production.

1.3 | Relative and combined interventions effects

NAC is supposed to optimize the effects of psychological interventions (Deepmala et al., 2015). However, with the exception of one randomized controlled trial (RCT) (McGorry et al., 2013), all pharmacological interventions so far were also offered in combination with some kind of psychological intervention, and CHR subjects in psychological trials were also allowed to take medication (Schmidt et al., 2015). Therefore, positive effects can neither be clearly attributed to one intervention nor do these studies allow any conclusions about their additive and combined effects.

Against this background, we aim to investigate the individual and combined preventive effects of two interventions in CHR subjects: (a) of an integrated preventive psychological intervention (IPPI) focusing on symptom/stress management and social-cognitive remediation and (b) NAC as a pharmacological intervention with glutamatergic, neuroprotective and anti-inflammatory capabilities.

2 | METHODS

2.1 | Design

This study is a 2 × 2-factorial trial (see Figure 1): A double-blind, placebo-controlled RCT with regard to NAC and a single-blind RCT with regard to IPPI. This serves to investigate the individual and combined preventive effects with NAC and IPPI as the experimental condition whereas placebo (Plc) and psychological stress management (PSM) serve as the control condition (see Figure 1). A total of 200 CHR subjects will be randomized (1:1:1:1) stratified by site to one of four conditions: (a) IPPI and NAC; (b) IPPI and Plc; (c) NAC and PSM; (d) Plc and PSM. Random assignment is implemented as a 24-7 internet service (ALEA; FormsVisionBV, Abcoude, NL; http://www.formsvision.com/). Allocation sequences are made from permuted blocks of varying length. Randomization results are given on screen and are sent by email to authorized members of staff. Interventions will be provided for 26 weeks including a follow-up period of 12 months with major assessments at baseline (week −4 to 0), beginning of intervention(s) after randomization (week 0), at week 12, at the end of intervention(s) (week 26), at 1-year follow-up (week 52) and end of follow-up (week 78) (see Table 1). The standard protocol items are provided in Table S1.

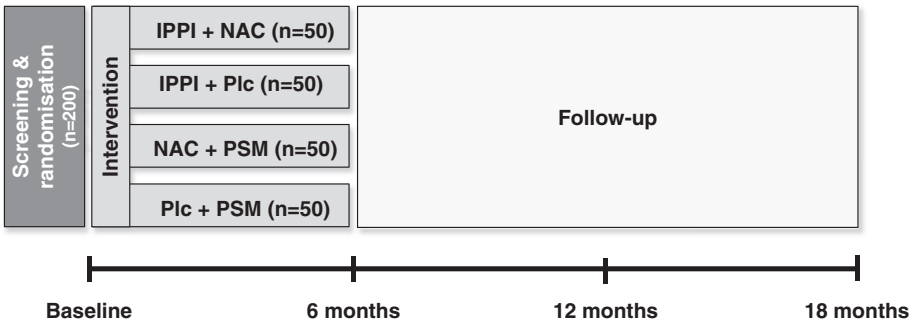

FIGURE 1 Study design. IPPI, integrated preventive psychological intervention; NAC, N-acetyl-L-cysteine; PSM, psychological stress management; Plc, placebo

2.2 | Setting

The project ESPRIT-B1 (ClinicalTrials.gov Identifier: NCT03149107) is part of the multi-trial "**E**nhancing **S**chizophrenia **P**revention and **R**ecovery through **I**nnovative **T**reatments" consortium (coordinator: Andreas Meyer-Lindenberg, Mannheim). ESPRIT is funded by the German Federal Ministry of Education and Research (BMBF) as part of the German Research Network for Mental Disorders and aims at developing and evaluating innovative interventions to: (a) prevent transition to schizophrenia in high-risk individuals, (b) enhance symptomatic and functional recovery in schizophrenia patients in the early phase of the illness and (c) implement these interventions in clinical practice. ESPRIT-B1 is a multi-centre study involving 11 centres in Germany with established early psychosis centres: RWTH Aachen, RH-FK Alzey, Charité and Vivantes Clinic Berlin, UK Bonn, UK Düsseldorf, MHH Hannover, UK Köln, ZI Mannheim, LMU München and UK Tübingen.

Study therapists trained in cognitive-behavioural therapy took part in a 2-day workshop on IPPI and PSM before the beginning of the study based on the respective manuals. All parts of this workshop are also available as teaching videos and arising problems were additionally discussed in telephone meetings following the workshop. Regular supervision is provided for raters and therapists separately in form of a monthly 1-hour telephone conference and additionally on individual basis via telephone or skype. Each session is audiotaped and rated by two independent individuals based on a well-established fidelity checklist (Haddock et al., 2001). Approval was obtained from the responsible federal agency (no. 4041081) and the ethic committees of all participating centres based on the trial protocol (January 2017).

2.3 | Sample

Inclusion, exclusion and withdrawal criteria of this study are shown in Table 2 and are in line with previous studies (Klosterkötter et al., 2005). Participants had to meet any ultra-high risk or basic symptom criterion as assessed by the Structured Interview for Psychosis-Risk Syndromes (SIPS 5.0; McGlashan et al., 2010) and the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter et al., 2007). Both assessments have shown good interrater-reliability (93% interrater agreement for SIPS and up to 91% for SPI-A), good test-retest reliability and construct as well as predictive validity (McGlashan et al., 2001; Miller et al., 2003; Schultze-Lutter et al., 2007, 2012, 2015). All interviewers (clinical psychologists or psychiatrists) received intensive 3-day training and monthly supervision by an international expert in early detection of psychosis. To ensure reliable and valid data, each participant will only be included in the study if ratings of the CHR symptoms are confirmed by the trainer. Each rating is discussed until consensus is reached. The study protocol does not include any reimbursement for the study participants.

2.4 | Interventions

2.4.1 | N-acetyl-L-cysteine and placebo

Both NAC and Plc are provided as two capsules of 500 mg twice a day, yielding a total dosage of 2000 mg per day. Dosage and mode of intervention were chosen in accordance with a recent trial (Berk et al., 2008) supporting the safety and efficacy of NAC in schizophrenia patients.

2.4.2 | Integrated preventive psychological intervention

IPPI was developed in a manualized form including four modules with the aim to: (a) provide disorder-related knowledge; (b) cope with stressors efficiently; (c) enhance understanding of and coping with current and future CHR symptoms and (d) improve social-cognitive information processing and social competencies (see Table 3). IPPI consists of 22 sessions (50 or 90 minutes) in an individual setting. The first 21 sessions are scheduled weekly with one booster session 2 weeks after the last session. Every module is organized in such a way to increase therapy motivation by activating an individual's resources, personalizing contents through selection of the most relevant strategies for each individual and by facilitating experimental learning using multi-sensory materials (eg, audios, videos of real-life situations, cartoons). Generalization of effects is enhanced in every module and in particular in the booster session by elaborating on the relevance of the respective target domain for everyday life, building upon and optimizing already existing strategies, discussing how to deal with potential barriers and by practising new skills in the natural environment between sessions as homework.

2.4.3 | Psychological stress management

PSM is based on the well-established relevance of stress and poor coping on the development of psychotic symptoms (Gomes & Grace, 2017). It is carried out in an individual setting as an active, manualized control condition to improve coping. PSM comprises 11 sessions, a

TABLE 1 Schedule of assessments

Instrument	Domain	Baseline Weeks (−4 to 0)[a]	Intervention period												Follow-up				
			0	2	4	6	8	10	12	14	16	18	22	26	30	39	52	65	78
Psychometric assessments																			
SIPS 5.0	Ultra-high risk criteria; negative, positive, disorganized and general symptoms		X		X		X		X					X			X		X
SIPS (5.0), P-scale	Transition to psychosis	X	X		X		X		X		X		X	X	X	X	X	X	X
SPI-A	Basic symptoms		X		X		X		X					X			X		X
SOFAS	Social and occupational functioning	X							X					X			X		X
FROGS	Functional recovery in daily and social life	X							X					X			X		X
GFsocial and GFrole	Social and school or work functioning	X	X						X					X		X	X	X	X
BNSS	Negative symptoms	X												X			X		X
TPA	Identification of main problems		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
M.I.N.I. 6.0	Diagnostic screening, Axis-I diagnosis	X												X			X		X
Questions about current substance use	Substance use behaviour	X	X		X		X		X		X		X	X	X	X	X	X	X
BSI-53	Symptom level and distress	X																	
CISS-24	Coping strategies	X												X			X		X
ESPRIT-WHO-QUOL	Health-related quality of life	X												X			X		
FETZ chart of life events	Current life events and evaluation	X							X					X			X		X
CTQ	Childhood abuse and neglect	X																	
RSA	Resilience	X												X			X		X
ISMI	Stigma	X												X			X		X
16-NFCS	Need for closure	X												X			X		X
ABF	Daily hassles		X											X			X		X
FKK	Self-efficacy and locus of control	X												X			X		X
ISK-K	Social skills	X												X			X		X
MASC	Social cognition, theory of mind	X												X			X		X
PoFA	Social cognition, emotion recognition	X												X			X		X
SAT-MC	Social cognition, social attribution	X												X			X		X
TMT A & B	Neurocognition, speed of processing, executive functions	X												X			X		X
AVLT	Neurocognition, verbal learning and memory	X												X			X		X

TABLE 1 (Continued)

Instrument	Domain	Baseline Weeks (−4 to 0)[a]	Intervention period												Follow-up				
			0	2	4	6	8	10	12	14	16	18	22	26	30	39	52	65	78
DSST	Neurocognition, speed of processing	X												X			X		
DS	Neurocognition, verbal memory	X												X			X		
MWT-B	Premorbid Intelligence	X																	
WHO disability assessment schedule	Disability	X																	
Safety and tolerability assessments																			
Neurologic and general examination		X												X					
Weight and height		X												X					
Pre-intervention symptoms (UKU symptom list)		X	X																
Adverse events (UKU symptom list)			X			X			X			X		X	X				
CDSS, complete		X							X					X			X		X
CDSS, items 1,2,8,9			X	X	X	X	X	X		X	X	X	X		X	X		X	
Laboratory assessments																			
Haematology/chemistry panels		X				X								X					
Urine/blood pregnancy test		X																	
Urine pregnancy test			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]					
Urine drug toxicology screening		X	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Treatment-related assessments																			
Psychiatric and medical history		X																	
Prior medication			X																
Concomitant treatment			X		X			X			X			X	X	X	X	X	X
Dispense/return study medication			X			X			X			X		X					
Reasons for study discontinuation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-reported treatment adherence						X			X			X		X					
DAI-10		X							X					X					
PATHEV		X		X					X					X					
Protocol of psychological interventions (therapist)			X	X	X	X	X	X	X	X	X	X	X	X					
Treatment allocation assumption (rater)			X		X		X		X		X		X	X	X	X	X	X	X
Additional assessments																			
MRI		X												X					
MRS— Blood sample (MRS genetics)		X												X					
Stool sample for microbiome		X												X			X		
Experience sampling (EMA)		X	X											X	X				

TABLE 1 (Continued)

Instrument	Domain	Baseline Weeks (−4 to 0)[a]	Intervention period												Follow-up				
			0	2	4	6	8	10	12	14	16	18	22	26	30	39	52	65	78
Health economic analyses (MRV; WHO-QoI-Bref)		X												X			X		
Biobanking (blood and saliva samples)		X												X					X
RDoC		X																	

Abbreviations: ABF, Daily Stress Inventory (Traue, Hrabal, & Kosarz, 2000); AVLT, Auditory Verbal Learning Test (Helmstaedter, Lendt, & Lux, 2001; Muller, Hasse-Sander, Horn, Helmstaedter, & Elger, 1997); BNSS, Brief Negative Syndrome Scale (Strauss et al., 2012); BSI-53, Brief Symptom Inventory-53 (Derogatis & Melisaratos, 1983); CDSS, Calgary Depression Scale (Addington, Addington, Maticka-Tyndale, & Joyce, 1992); CISS-24, Coping Inventory for Stressful Situations (Endler & Parker, 1990); CTQ, Childhood Trauma Questionnaire (Scher, Stein, Asmundson, McCreary, & Forde, 2001); DAI, Drug Attitude Inventory (Hogan, Awad, & Eastwood, 1983; Nielsen, Lindström, Nielsen, & Levander, 2012); DS, Digit Span (Petermann & Petermann, 2010); DSST, Digit Symbol Substitution Test (Petermann & Petermann, 2010); ESPRIT-WHO-QUOL, Questionnaire World Health Organization Quality of Life (TheWhoqolGroup, 1998); FKK, Germen Questionnaire on Competence and Control beliefs (Krampen, 1991); FROGS, Functional Remission of General Schizophrenia (Llorca et al., 2009); GFS/GFR, Global Functioning Scale: Social and Global Functioning: Role (Cornblatt et al., 2007; Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000); ISK-K, Inventory of Social Competencies-short version (Kanning, 2009); ISMI, Internalized Stigma of Mental Illness Scale (Sibitz et al., 2013); MASC, Movie for the Assessment of Social Cognition (Dziobek et al., 2006; Montag et al., 2011); M.I.N.I. 6.0, Mini International Neuropsychiatric Interview (Sheehan et al., 2010); MRI, magnetic resonance imaging; MRS, Magnetic resonance spectroscopy; MRV, Mannheim Service Use Questionnaire (Salize & Kilian, 2010); MWT-B, Multiple Choice Word Test-B (Lehrl, 1999); NFCS, Need for Closure Scale-16 (Schlink & Walther, 2007); PATHEV, Patient Questionnaire on Therapy Expectations and Evaluation (Schulte, 2005); PoFa, Picture of Facial Affect Test (Bölte et al., 2002); RDoC, Research Domain Criteria; RSA, Resilience Scale for Adults (Resnick & Inguito, 2011); SAT-MC, Social Attribution Test-multiple choice (Bell, Fiszdon, Greig, & Wexler, 2010); SIPS, Structured Interview of Prodromal Syndromes (McGlashan, Walsh, & Woods, 2010); SPI-A, Schizophrenia Proneness Instrument, Adult Version (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007); SOFAS, Social Functioning Assessment Scale (APA, 2000); TMT A & B, Trial Making Test A & B (Reitan, 1958); TPA, Top Problem Assessment (Weisz et al., 2011); UKU side-effect rating scale (Lindström et al., 2001).

[a] During intervention +/− 4 days, during follow-up +/− 2 weeks, deviations from starting date do not sum up.

[b] In case of suspected pregnancy.

[c] Additionally, if transition assessment is positive (SIPS 5.0 P-Scale); interviews and ratings carried out by clinicians (ie, SIPS, SPI-A, SOFAS, FROGS, GFsocial/GFrole, BNSS) will take at baseline around 90 minutes, questionnaires 45 minutes, neuro- and social-cognitive assessments 75 minutes; MRI and MRS assessments 60 minutes each, blood and stool samples 10 minutes and experience sampling around 5 minutes each time.

50 minutes (10 bi-weekly sessions; last session 2 weeks later) (see Table 4).

2.4.4 | Prior and concomitant interventions

All previous interventions to manage the trial-specific illness are documented in an electronic case report form (CRF). With regard to indications other than the trial-specific illness, all previous interventions are allowed and documented in the CRF for the past 3 months before the beginning of the trial. With regard to concomitant interventions, the short-term administration of lorazepam or oxazepam for acute agitation as well as zolpidem, zopiclon or temazepam for sleep disturbances is allowed. Any intake of antipsychotic and/or mood stabilizing medication and/or pregabalin and/or the use of antitussives and nitroglycerin are prohibited during the whole trial period. All concomitant psychological and/or pharmacological interventions for other indications are administered in line with current treatment guidelines and documented in the subject's study record and CRF.

2.4.5 | Blinding of interventions

Packaging, appearance, colour and taste of the capsules of NAC and Plc are identical to ensure blinding. To maintain blindness of raters, they have access to the (anonymous) patient- and therapy-ID only. Furthermore, IPPI and PSM will be carried out independently from assessors, who are kept unaware of the treatment allocation during all times of the trial. To avoid any form of communication between therapists and assessors, they are not allowed to talk about study subjects with each other and have separate offices as well as study procedures. Study subjects are instructed not to disclose aspects of their intervention to the assessors. Assessors are asked to record any loss of masking of treatment allocation and are asked to guess the allocation.

3 | HYPOTHESES

1. Both NAC and IPPI produce significant effects on transition rates to psychosis and significant improvements in social functioning as primary outcomes compared to control conditions.
2. Both NAC and IPPI produce significant improvements in neuro- and social-cognitive domains as secondary outcomes relative to control conditions.
3. Combined effects of NAC and IPPI on primary and secondary outcomes are significantly larger than those of NAC or IPPI alone.
4. IPPI is hypothesized to produce significantly larger effects on social cognition and social functioning than NAC and PSM.
5. Comparable tolerability is hypothesized for NAC and IPPI.

4 | STUDY OUTCOMES

4.1 | Primary study outcomes

Primary outcomes are both transition to psychosis defined as the presence of at least one psychotic symptom for at least 1 week and social functioning after 18 months (see Table 1).

TABLE 2 Inclusion, exclusion and withdrawal criteria of the study

Inclusion criteria

1. Age between 18 and 40 years
2. Subjects with the ability to follow study instructions and to attend as well as complete all required visits
3. Written informed consent of the subject
4. Clinical high risk criteria
   - ESPRIT Ultra-high risk criteria (Attenuated positive symptoms and/or brief limited psychotic symptoms and/or a combination of familial risk or schizotypal disorder with a significant loss of functioning; severity assessed by the Structured Interview for Prodromal Syndromes, SIPS 5.0, McGlashan et al., 2010)
   - The Basic Symptom Criterion "Cognitive disturbances" (COGDIS) (2/9 cognitive-perceptive basic symptoms; assessed by the Schizophrenia Proneness Instrument, Adult Version, SPI-A, Schultze-Lutter et al., 2007)

Exclusion criteria

Subjects will not be included in the study if any of the following criteria apply:

1. Known history of hypersensitivity to the investigational drug or drugs with a similar chemical structure
2. Simultaneous participation in another clinical trial investigating medical products within 30 days prior to beginning of this clinical trial. Simultaneous participation in a non-interventional trial is permitted in case the subject is nevertheless willing and able to attend and complete in all required visits of the trial and in case there are no other contradictions
3. Subjects with a physical or psychiatric condition which at the investigator`s discretion may put the subject at other clinically significant risks than those defined as outcome of this study (ie, development of a first-episode of psychosis, functional deterioration), may confound the trial results, or may interfere with the subject's per protocol participation in this clinical trial
4. Suicidality in terms of subjects scoring higher than 0 on the Calgary Depression Scale for Schizophrenia item 8 on "suicidality"
5. Subjects with known substance abuse or dependency (DSM-IV-TR)
6. Subjects with hepatic or renal failure
7. Subjects with known problems of galactose intolerance, clinically significant lactase deficiency or glucose-galactose malabsorption or histamine-intolerance of asthma bronchiale
8. Subjects with known asthma bronchiale
9. Subjects with a history of gastrointestinal ulcer
10. Intake of antitussives (cough-relieving agents)
11. Intake of nitroglycerin

Exclusion criteria regarding special restrictions for females

12. Current pregnancy or pregnancy planned within 9 months after start of medication or nursing women
13. Females of child-bearing potential, who are not using and not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable or implantable contraceptives or intrauterine devices) unless they are surgically sterilized/hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases

Indication-specific exclusion criteria

14. Having had a psychotic episode for more than 1 week (according to SIPS 5.0, McGlashan et al., 2010)
15. Having symptoms relevant for inclusion potentially arising from a known general medical disorder
16. Life-time antipsychotic medication for more than 30 days (cumulative number of days) at or above minimum dosage for a "first-episode of psychosis" range according to current German treatment guidelines (exception: maximum dosage for aripiprazole is 5 mg/d)
17. Any intake of antipsychotic medication (ie, independent of duration of intake) within past 3 months before psychopathological baseline assessments (including self-ratings and screening assessments) at or above minimum dosage of the "first-episode of psychosis" range according to current German treatment guidelines
18. Any intake of mood stabilizers (lithium, valproate, carbamazepine, oxcarbazepine, lamotrigine) for more than 30 days (cumulative number of days) during the past 3 months or any intake during the month before psychopathological baseline assessments (including self-ratings and screening assessments)
19. Any past psychotherapeutic treatment specifically targeting psychotic symptoms or its prevention

Withdrawal criteria

1. Investigator considers that because of safety, behavioural or administrative reasons, the subject needs to be excluded from the trial
2. New toxicological or pharmacological or severe adverse events occur that invalidate the earlier risk-benefit ratio; written informed consent of the subject
3. Study-participant develops a manifest psychotic disorder (SIPS 5.0, McGlashan et al., 2010)

4.2 | Secondary study outcomes

As secondary outcomes, we investigate effects on remission of CHR criteria (ie, attenuated psychotic symptoms, brief intermittent psychotic symptoms and/or cognitive basic symptoms (cognitive disturbances, COGDIS) and decrease in overall positive, negative, disorganization and depressive symptoms (see Table 1). Furthermore, changes in neuro- and social-cognitive domains and the following treatment-related variables will be assessed: dispense/return of study medication, reasons for study discontinuation, self-reported treatment adherence and reported expectations as well as evaluation regarding treatment. Moreover, safety and tolerability of interventions are evaluated by: (a) neurologic and general examination; (b) adverse events (AEs) and (c) laboratory assessments. AEs will be summarized by MedDRA code, relatedness, seriousness and severity. Any AE relevant for the evaluation of the clinical trial has to be documented in the CRF. Every serious adverse event (SAE) between the first intake of study medication and 30 days after the last administration of study medication must be documented in the CRF and on the SAE report form. The investigator has to report any SAE within 24 hours and every pregnancy during the clinical trial to the Clinical Trials Centre Cologne. All cases of Suspected Unexpected Serious Adverse Reactions (SUSARs) during the study have to be reported to the responsible supreme federal authority and the respective ethics committee and to all clinical trials investigators of the same active substance.

4.3 | Additional study outcomes

Additional outcomes (see Table 1) are the following: (functional) magnetic resonance imaging (fMRI) to investigate functional and structural abnormalities while performing psychological tasks; magnetic resonance spectroscopy (MRS) and blood tests to determine whether

TABLE 3 Content and intervention techniques of the integrated preventive psychological intervention (IPPI)

Session number	Target domain	Intervention techniques
1	Introduction; Problems and resources	• Forming a therapeutic relationship • Exploration of current risk-symptoms and other mental health problems • Functionality of risk-symptoms for social environment and educational/job performance • Introduction of the intervention model and modules of the IPPI • Elaboration of main difference between diagnosis and risk • Identification of main resources and problems of each individual
2	Explanation model and psychoeducation	• Formulation of an individual explanation model for an at-risk state for psychosis • Linking individual risk-symptoms to the aims of IPPI and integrate them in overall intervention plan • Exploring possible misunderstandings and negative expectations related to the explanation model
3-5	Stress management	• Repetition of explanation model • Linking stressors to risk-symptoms • Introduction of concepts and models of stress and coping • Identifying external/internal triggers of stress, functionality of stress and stress reactions of each individual • Exploring and providing feedback on the individual coping profile • Introduction and practice of the following coping-strategies: mindfulness, progressive muscle relaxation and setting priorities
6-11	Symptom management	• Linking risk-symptoms to the individual explanation model • Normalizing and validation of emotions related to risk-symptoms • Psychoeducation about different groups of risk-symptoms (basic symptoms, unusual and delusional thought contents, attenuated hallucinations and self-disturbances) by discussing current explanation models • Formulation of an individual explanation model of risk-symptoms including autobiographical aspects • Optimizing and practising cognitive-behavioural strategies to reduce risk-symptoms (eg, modification of stressors, cognitive biases and dysfunctional schema; generation of alternative explanations and experiments for reality testing) and emotion-focused strategies to deal with emotions triggered by risk-symptoms (eg, anxiety, anger, depressiveness); cognitive remediation strategies to target deficits in selective attention and inhibition related to basic symptoms and aberrant salience processing
12-15	Social cognition—affect recognition	• Optimizing decoding of emotions including facial expressions, gesture and prosody based on exercises with increasing speed and intensity of emotions • Imitation of emotional expressions using a mirror • Computerized exercises to improve automatization of decoding processes
16	Social cognition—social perception	• Identification and training of strategies to identify relevant social signals to interpret interpersonal situations with increasing complexity • Practising strategies based on a series of photos of social interactions to identify and use core social signals (eg, distance, mutual affection, value of interaction, social roles)
17	Social cognition—theory of mind and empathy	• Optimizing and practising strategies to enhance theory of mind/empathy based on video-taped social interactions (eg, to understand ironic messages) • Role-play of difficult social interactions to identify thoughts and feelings of others
18-19	Social cognition—social attributions	• Psychoeducation about common attribution biases (eg, hostile attribution bias) • Linking attribution biases to deficits in theory of mind/empathy, one's own self-concept and self-stigma • Identification of cognitive, emotional and social consequences of attribution biases • Exploration of attribution styles based on case-vignettes and own attribution biases in everyday life • Generation of alternative attributions
20-22	Social: Problem-solving and booster session	• Applying all learned social-cognitive strategies to complex social interactions • Discussing difficulties experienced when applying strategies in natural environment • Summarizing intervention contents and most important resources and strategies of each individual

NAC effectively elevates glutathione levels; and experience sampling to collect participants' responses to questions regarding mood, symptoms, social context, stress, sleep and current location using geo-localizing at the beginning and after the intervention. Furthermore, health economic analyses are conducted to evaluate the cost-effectiveness of these interventions. Biographical, neuropsychological and psychopathology data are clustered using multivariate cluster analysis (RDoC), which yields subgroups of individual variation across these variables within the population under study. Each subject's likelihood of belonging to such a subgroup is used to explore differences in intervention effects as a function of syndrome constellations. Faecal samples are taken before and after intervention for molecular characterization using 16S rRNA gene sequencing to investigate whether aberrations in microbial community structure and function as well as changes in these variables as a function of treatment condition predict transition to psychosis.

5 | STATISTICAL ANALYSES

5.1 | Power

Based on recent publications (Schultze-Lutter et al., 2015), we assume a transition risk of about 20% within 18 months. We expect a relative reduction in transition risk of 80% (Schmidt et al., 2015; Van der Gaag et al., 2013), that is, from 20% to 4%. To detect this difference with 80% power at two-sided level 2.5% (ie, Bonferroni-corrected for two comparisons), an uncorrected χ^2 test needs 77 subjects per group. Using the actual time-to-event, the power of corresponding hypothesis tests (ie, log-rank test, Cox regression) is expected to be slightly higher (Pocock, 1983). To compensate for the influence of about 25% drop-out, 100 CHR subjects per group (ie, 200 CHR subjects in total, 50 per cell) will be included (see Figure 1).

TABLE 4 Content and intervention techniques of the psychological stress management (PSM)

Session number	Target domain	Intervention techniques
1	Introduction; Problems and resources	• Forming a therapeutic relationship • Exploration of current risk-symptoms and other mental health problems • Functionality of risk-symptoms for social environment and educational/job performance • Introduction of the intervention model and modules of PSM • Identification of main resources and problems of each individual
2	Explanation model and psychoeducation	• Formulation of an individual explanation model for an at-risk state for psychosis • Elaboration of main difference between diagnosis and risk • Linking individual risk-symptoms to the aims of PSM and integrate them in overall intervention plan • Linking the influence of stress to the individual explanation model • Exploring possible misunderstandings and negative expectations related to the explanation model
3	Concepts and models of stress	• Repetition of explanation model • Linking stressors to risk-symptoms • Psychoeducation about concepts and models of stress and coping • Identifying external/internal triggers of stress, functionality of stress and stress reactions of each individual
4	Internal triggers of stress	• Repetition of concepts and models of stress • Identifying internal triggers of stress • Exploring positive and negative consequences of the individual internal triggers of stress • Introduction of concepts and models of coping
5	Individual coping profile	• Repetition of concepts and models of coping • Exploring and providing feedback on the individual coping profile
6	Setting priorities	• Exploring positive and negative consequences of individual coping-strategies • Elaboration of differences between functional and dysfunctional coping-strategies • Introduction and practising of setting priorities as a functional coping-strategy • Training of setting priorities in everyday life
7	Mindfulness	• Optimizing the use of setting priorities as a coping-strategy • Introduction of mindfulness as a functional coping-strategy • Practising applying mindfulness-based exercises • Training of mindfulness in everyday life
8	Progressive muscle relaxation	• Optimizing the use of mindfulness as a coping-strategy • Introduction of progressive muscle relaxation as a functional coping-strategy • Practising of progressive muscle relaxation • Training of progressive muscle relaxation in everyday life
9	Optimizing coping-strategies I	• Optimizing the use of progressive muscle relaxation as a coping-strategy • Integration in the individual coping profile • Exploring the Top 5 coping-strategies • Continuous training of progressive muscle relaxation
10	Optimizing coping-strategies II	• Training of an individual functional coping-strategy • Applying the Top 5 coping-strategies to everyday life
11	Booster session	• Discussing difficulties experienced when applying strategies in natural environment • Linking stressors to risk-symptoms • Summarizing intervention contents and most important resources and strategies of each individual

5.2 | Data management

Data management and monitoring infrastructure will be supplied by the Clinical Trials Centre Cologne. Data will be entered online at the trial sites. All changes made to the data are documented in an audit trail. After completion and cleaning of data, the database is locked and the data are stored and exported for statistical analysis by the Clinical Trials Centre.

5.3 | Data analyses

The full analysis set will be based on the intention-to-treat principle. The primary endpoint "transition within 18 months" will be analysed by time-to-event methods, that is, Cox regression with main effects NAC, IPPI, age and gender; no interactions. Hazard ratios and corresponding 97.5% confidence intervals will be determined. The co-primary outcome variables improvement of social functioning after 18 months will be analysed using mixed models for repeated measures (MMRM; fixed effects baseline, NAC, IPPI, time, NAC*time, IPPI*time) with corresponding contrasts. Patterns of missing values will be investigated and the impact of various strategies for handling the missing values will be explored in a sensitivity analysis. Subgroup analyses will be done by centre and gender including exploration of possible interactions with interventions. Secondary outcomes will be analysed either by time-to-event methods, MMRM or using generalized estimating equations to describe and evaluate differences between groups and changes over time. Any clustering effects due to same care providers and centres will be investigated in sensitivity analyses (Boutron et al., 2008).

6 | DISCUSSION

This paper presents the study rationale and methodology of a large-number multi-centre prevention study in CHR subjects. The study includes two different types of novel interventions: An IPPI with special emphasis on social cognition to complement and broaden current cognitive-behavioural intervention approaches and a novel

pharmacological agent (NAC) with potential neuroprotective effects through its impacts on dysfunctional glutamatergic neurotransmission. The 2 × 2-factorial design of the study is intended to detect beneficial combinations of these interventions on several outcomes encompassing transition rate, social functioning, risk and general symptoms, social- as well as neuro-cognitive performance and overall tolerability of these interventions. Together with additional data on potential biomarkers and neurobiological mechanisms, our results may support efforts to further personalize interventions for CHR patients by matching intervention techniques to individual risk constellations and mechanisms of change. Potential limitations of this trial include the large number of assessments and exclusion criteria, which may pose difficulties to the recruitment process, and the overlap of contents between IPPI and PSM. Taken together, this trial is expected to provide new and well-tolerated interventions, thus helping to lower the individual and societal burden of psychotic disorders.

ACKNOWLEDGEMENTS

This study is funded by the German Federal Ministry of Education and Research (BMBF) (project numbers: 01EE1407C, 01EE14071). ESPRIT-B1 Group: Bechdolf, A (Berlin Vivantes); Brockhaus-Dumke, A (RH-RF Alzey); Hirjak, D (ZI Mannheim); Fallgatter, A (UK Tübingen); Frieling, H (MHH Hannover); Janssen, B (UK Düsseldorf); Jessen, F (UK Köln); Kambeitz, J (LMU München); Koutsouleris, N (LMU München); Leopold, K (Vivantes Berlin); Schäfer, C (UK Bonn); Schultze-Lutter, F (UK Düsseldorf); Striepens, N (UK Bonn); Vernaleken, I (RWTH Aachen); Walter, H (Charité Berlin) and Wildgruber, D (UK Tübingen).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Schmidt SJ, Hurlemann R, Schultz J, et al. Multimodal prevention of first psychotic episode through N-acetyl-L-cysteine and integrated preventive psychological intervention in individuals clinically at high risk for psychosis: Protocol of a randomized, placebo-controlled, parallel-group trial. *Early Intervention in Psychiatry*. 2019;1–12. https://doi.org/10.1111/eip.12781