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Rationale and Baseline Characteristics of PREVENT: A Second-Generation Intervention Trial in Subjects At-Risk (Prodromal) of Developing First-Episode Psychosis Evaluating Cognitive Behavior Therapy, Aripiprazole, and Placebo for the Prevention of Psychosis

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Antipsychotics, cognitive behavioral therapy (CBT), and omega-3-fatty acids have been found superior to control conditions as regards prevention of psychosis in people at-risk of first-episode psychosis. However, no large-scale trial evaluating the differential efficacy of CBT and antipsychotics has been performed yet. In PREVENT, we evaluate CBT, aripiprazole, and clinical management (CM) as well as placebo and CM for the prevention of psychosis in a randomized, double-blind, placebo-controlled trial with regard to the antipsychotic intervention and a randomized controlled trial with regard to the CBT intervention with blinded ratings. The hypotheses are first that CBT and aripiprazole and CM are superior to placebo and CM and second that CBT is not inferior to aripiprazole and CM combined. The primary outcome is transition to psychosis. By November 2010, 156 patients were recruited into the trial. The subjects were substantially functionally compromised (Social and Occupational Functioning Assessment Scale mean score 52.5) and 78.3% presented with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* axis I comorbid diagnosis. Prior to randomization, 51.5% of the participants preferred to be randomized into the CBT arm, whereas only 12.9% preferred pharmacological treatment. First, assessments of audiotaped treatment sessions confirmed the application of CBT-specific skills in the CBT condition and the absence of those in CM. The overall quality rating of the CBT techniques applied in the CBT condition was good. When the final results of the trial are available, PREVENT will substantially expand the current limited evidence base for best clinical practice in people at-risk (prodromal) of first-episode psychosis.

Key words: schizophrenia/aripiprazole/cognitive behavior therapy/prodrome/early intervention/prevention/psychosis

Introduction

Early detection and intervention strategies have led to substantial improvement of the prognosis of a number of nonpsychiatric medical conditions.[1–3] The significant personal, social, and financial costs of schizophrenia provide the primary rationale for adapting these strategies for schizophrenia. Recently, reliable criteria based on subthreshold levels of psychotic symptoms (ultra high-risk [UHR] criteria)[4–6] and/or on subtle, subjective, subclinical cognitive-perceptive disturbances (basic

symptoms [BS])[7,8] have been to identify an at-risk population and to predict psychosis onset within 12 months in 20%–30% of cases.[8,9,10] Effective interventions for individuals meeting these criteria are needed in order to reduce or prevent the devastating effects of the disorder.[11]

Six randomized controlled trials (RCTs) in the at-risk population have been completed so far. They have included evaluations of low-dose risperidone and cognitive behavioral therapy (CBT) combined,[12] CBT[13,14] or an integrated psychological intervention,[15] olanzapine,[16] and omega-3-fatty acids.[17] The results of the treatment phase indicated advantages on a descriptive level[14,16] or significant results[12,13,15,17] in favor of the respective experimental condition.

However, due to a number of methodological limitations, the empirical evidence of the superiority of CBT or antipsychotics to unspecific control conditions is preliminary. These limitations are as follows: (a) inadequate or unclear concealed treatment allocation,[12,15] (b) exclusion of participants after randomization,[13] and (c) lack of blinded ratings.[12,13] Interpretation and generalizability of the RCTs mentioned above are further limited by (a) not reporting the population assessed for eligibility[16] and the reasons for nonparticipation in those meeting inclusion criteria[12,13,16]; (b) a bias toward a population with lower psychosis incidence in the Morrison study when compared with the other studies using UHR criteria (transition rate in control condition: 36%,[12] 38%,[16] and 22%[13]); (c) sample sizes that are too small to detect significant differences between trial conditions for the active treatment sample over a 12-month period (n = 59,[12] n = 60,[16] n = 51[14]); (d) trial design, which does not allow the assessment of the relative contribution of antipsychotics and of CBT,[12]; (e) the lack of standardized psychosocial interventions[16]; (f) the use of assessment instruments that have not been evaluated for people at-risk[12]: Brief Psychiatric Rating Scale[13] and Positive and Negative Syndrome Scale (PANSS)[13,17]; and (g) not measuring the integrity of CBT.[12,13,15] In accordance with the literature,[18,19] RCTs performed with lower methodological quality were more likely to report significant advantages for the respective specific interventions, whereas 2 of the 3 trials with high scientific rigor so far reported the specific intervention to be superior to unspecific treatment only on a descriptive level.[16,14] Moreover, data on safety and tolerability of antipsychotics in the at-risk population are sparse.

In addition, no information on the differential efficacy of CBT or antipsychotics in people at-risk of psychosis is available. It has been argued that CBT may have some advantages compared with antipsychotics such as[20,21] (a) being more acceptable, tolerable, and less stigmatizing to clients[22,23]; (b) removing the risk of exposing false positives to pharmacological side effects; and (c) providing effective treatment for false positives (depression and anxiety disorders). Further evidence suggests treatment effects in clients with schizophrenia.[24] Therefore, many authors call for methodologically sound, collaborative, large-scale RCTs on indicated prevention in people at-risk of psychosis involving psychological and pharmacological preventive strategies.[25,26,27,28,29]

Considering ethical, acceptance, and compliance considerations and drawing on the first evaluations of indicated prevention in people at-risk of psychosis, the study addresses the following research questions with high methodological rigor[1]: Are clinical management (CM) and aripiprazole combined more effective in people at-risk of psychosis than CM and placebo combined?[2] Is CBT more effective in people at-risk of psychosis than CM and placebo combined?[3] Is CBT not less effective in people at-risk of psychosis than CM and aripiprazole combined?

When the final results of the trial are available, PREVENT will substantially expand the current limited evidence base for best clinical practice in people at-risk (prodromal) of first-episode psychosis. The aim of the present article is to present rationale, design, and baseline characteristics of the PREVENT trial.

Methods

The protocol was approved by the respective institutional review boards at the trial sites. All participants provided written informed consent prior to any research activity. This study is registered with the identifier ISRCTN: 02658871.

Setting and Subjects

The study takes place at 9 Early Detection and Intervention Centres located at the Departments of Psychiatry and Psychotherapy at the Universities of Cologne, Bonn, Aachen, Düsseldorf, Bochum, Hamburg, Göttingen, München, and Berlin. All centers serve as specialized outpatient departments and are designed to provide a low-threshold, nonstigmatizing environment. An awareness program is conducted, which aims to engage persons at-risk with the early intervention services. Referrals are taken from primary health care, mental health professionals, counseling services, and other support services or by self- or family referral. Referrals are screened with an Inclusion Criteria Checklist (ICC) and assessed in more detail with the Structured Interview for Prodromal Symptoms (SIPS)/Scale of Prodromal Symptoms (SOPS)[4] when they meet ICC inclusion criteria or are close to meeting inclusion criteria and not meeting exclusion criteria.

For PREVENT, we aim at further concentrating and at the same time reducing the number of false positives of the UHR criteria by adding an additional at-risk group.[30] For this purpose, the ''cognitive disturbances''—cluster of the BS (COGDIS) was chosen because it was associated with a transition rate of 23.9% at 12 months and

Table 1. Inclusion Criteria

Age between 18 and 40 y
Belong to one or more of the following groups:
(1) Attenuated positive symptoms—Presence of at least one of the following symptoms (SOPS scores 3–5): Unusual thought content/delusional ideas, suspiciousness/ persecutory ideas, grandiosity, perceptual abnormalities/ hallucinations, disorganized communication.
(2) Brief limited intermittent psychotic symptoms—Presence of at least one of the following symptoms $\leq$7 days resolving spontaneously (SOPS score = 6): Hallucinations, delusions, formal thought disorder. There can also be several different symptoms with a SOPS score = 6 that occur consecutively in a time span $\leq$7 days resolving spontaneously.
(3) Predictive basic symptoms—Presence of at least 2 of the 9 following symptoms (Schizophrenia Prediction Instrument—Adult Version $\geq$ 3) during the last 3 mo and a presence for more than 1 y: Inability to divide attention, thought interferences, thought pressure, thought blockages, disturbance of receptive speech, disturbance of expressive speech, disturbance in abstract thinking, unstable ideas of reference, captivation of attention by details of the visual field.
(4) Family risk plus reduced functioning: A first-degree relative with a history of any *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) psychotic disorder or DSM-IV schizotypal personality disorder of the index person and a change in mental state or functioning leading to a reduction of 30% or more on the Global Assessment of Functioning (GAF) Scale for at least 1 mo within the last year compared with the highest level of previous functioning.

46.3% at 24 months.[8] This procedure corresponds to the inclusion criteria of the European Prediction of Psychosis Study.[31] This study, comprising 245 help-seeking individuals, found that the combination of UHR and COGDIS criteria was associated with higher transition rates than those of each group separately (table 1).[9]

The main exclusion criteria are as follows: Current or past antipsychotic treatment for longer than 1 week, previous psychotic episode for longer than 1 week, current suicidality or dangerous behavior, alcohol or substance dependence, organic brain disease, IQ $<$ 70, living out of area, other medical reasons like current or intended pregnancy, lactation or missing reliable method of contraception, taking drugs with anticipated interactions, etc.

Study Design

PREVENT is a parallel group RCT with 3 study conditions: A randomized, double-blind, placebo-controlled trial with regard to the antipsychotic intervention and a RCT with regard to the CBT intervention with blinded ratings. All interventions are delivered over a 12-month period.

Randomization

All patients are screened and documented in a screening log. Treatment is assigned to patients who fulfill all inclusion and no exclusion criteria and have given written informed consent. The randomization code is computer generated for balanced (restricted) randomization with balance points defined through blocks, which realize the allocation ratio 3:5:7. Random assignment is stratified using the Montgomery-Asberg Depression Rating Scale (MADRS, total score $<$ 21 or $\geq$ 21), as depressive symptoms may affect illness progression[32] as well as treatment with antidepressants.[33] A computer-generated random sequence based on a block-randomized design is kept in a remote secure location and administered by an independent third party until all study data are collected and verified.

Study Interventions

Aripiprazol and Clinical Management (CM) Aripiprazol is the chosen antipsychotic because of its partial dopamine D_2 and 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist activity. Aripiprazole is as effective as other antipsychotics and has good tolerability, especially with regard to hyperprolactinemia, sedation, weight gain, diabetes mellitus, electrocardiographic disturbances, and extrapyramidal symptoms.[34,35] First, pilot evaluations in people at-risk of psychosis demonstrated a good efficacy and tolerability of the compound.[36,37] In accordance with the literature of people at-risk,[12,38] the dose is lower ranging from 5 to 15 milligrams per day. A total of 20 CM sessions is provided (weekly in the first 4 weeks, biweekly in the second 3 months, and monthly over the following 8 months). The initial session is 45–60 minutes, with other sessions of 20–30 minutes. The content of sessions is detailed in a manual.[39] The elements of CM are as follows: psychoeducation on at-risk mental state syndrome, pharmacotherapy, side effects of pharmacotherapy, monitoring target symptoms and possible side effects, and providing advice. A specific algorithm based on a checklist covering key symptoms and side effects is provided to decide on dosage adjustment of aripiprazole/placebo. CM and CBT share psychoeducation, but beside this, in the CM condition, CBT strategies or homework tasks are not allowed.

Cognitive Behavioral Therapy (CBT). A total of 30 individual 50-minute CBT sessions over the 12-month period is provided. CBT is provided weekly for the first 4 months, biweekly over next 6 months, and monthly over the last 2 months of the intervention. However, the frequency and duration of the sessions is flexible depending on arrangements made between the individual clients and the therapists as well as on the mental state of individual clients. The intervention is detailed in an individual therapy manual by Bechdolf and coworkers.[40,41] This manual is based on one developed for an earlier trial, which involved identifying people at-risk in accordance with the BS criterion cognitive-perceptive criteria.[8] It was found

to be feasible and accepted by clients and therapists.[15] The related manual was revised and supplemented according to the extended inclusion criteria of the present trial with specific strategies to address the additional BS included in the COGDIS cluster, attenuated positive symptoms, and brief limited intermittent psychotic symptoms. Based on an integrative cognitive model,[42–44] the individual CBT follows the basic principles of cognitive therapy described by Beck[45] as being formulation driven, structured, based on shared problems and goals, educational, as utilizing guided discovery as the engine for change, involving homework, and being time limited. Depending on the problems presented and the case formulation, therapists adapt the modules detailed in the manual. The applied cognitive behavior strategies are as follows: formulation; collaborative goal setting; provision of information and education about stress, BS and negative symptoms, depression, and anxiety; stress-monitoring; relaxation techniques; distraction techniques; self-monitoring of symptoms; normalizing (attenuated) psychotic experiences; change strategies; generating and evaluating alternative explanations; behavioral experiments; thought monitoring; cognitive restructuring; positive coping; positive reframing and challenging; goal setting and time management; coping enhancement techniques; normalizing self-experience of neuropsychological deficits; behavioral strategies such as thought stopping, distraction, and activity scheduling; exposure techniques; cognitive restructuring of negative and self-defeating cognitions; relapse prevention; scheduling and monitoring of mastery and pleasure activities; keeping well strategies; assertiveness and social skills training; and problem solving. (For an overview of the relevant CBT approaches, see Bechdolf et al.[21])

Placebo and CM. Because variability is reported in the transition rates of people at-risk,[46] to establish the efficacy of aripiprazole and CBT, it is important to include a placebo condition in the present design to indicate the transition rate using nonspecific strategies. In addition, the pill placebo may also provide a partial control condition against which to compare CBT. The CM component thus approximates a ''minimal supportive therapy'' condition, and the placebo condition serves as a control both for the expectations due to administration of a drug and for contact with a caring, supportive therapist. This condition thus provides a most stringent test of the specific efficacy of the psychotherapy condition. CM will be provided as described in the aripiprazole + CM condition.

Primary Outcome

The primary endpoint is ''transition to psychosis.'' The event transition to psychosis is operationalized in accordance with McGlashan[16] and Addington[14] by one or more of 5 SOPS-positive items rated with score = 6 longer than 7 days. The reliability of this or a similar operationalization has been assessed in reliability studies and, after a period of training, has been judged to be good or excellent.[1,9,12] Clients presenting with these scores exit the RCT as completers, and treatment with open label aripiprazole or another antipsychotic is recommended. These transition criteria carry the limitation that between 40% and 50% of all persons meeting them later develop psychotic disorders different from schizophrenia.[5,6,9] However, the criteria were designed on a pragmatic basis and in the interest of care and protection of research participants. They are meant to define the minimal point at which antipsychotic treatment might be indicated. There is agreement between the researchers in the area that this definition (or a similar one) presents a threshold at which second-generation antipsychotic medication should normally be commenced and applies equally well to substance-related symptoms, symptoms that have a mood component—either depression or mania—and schizophrenia spectrum disorders. The further specification of the psychotic syndrome as *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) 295.1–4, 295.7, 295.9, 296.04, 296.24, 296.34, 297.1, and 298.8 will be assessed by a Structured Clinical Interview for Diagnostic and Statistical Manual IV Axis I Disorders (SCID I) interview at least 4 weeks after meeting transition criteria and completing the study.

Secondary Outcomes and Measures

Secondary outcome measures are time to transition, psychopathological symptoms, social functioning, subjective quality of life, and side effects of medication as measured by the following: SIPS/SOPS,[4] Schizophrenia Prediction Instrument—Adult Version (SPI-A),[47] PANSS,[48] MADRS,[49] Beck Depressions Inventory,[45] State Trait Anxiety Inventory,[50] Modular System for Quality of Life,[51] Social and Occupational Functioning Assessment Scale (SOFAS),[52] Social Adjustment Scale,[53] Udvalg for Kliniske Undersøgelser Side Effect Rating Scale,[54] and Extrapyramidal Symptom Rating Scale.[55] Moreover, at baseline, SCID I and SCID II (axis I + II disorders) interviews are performed as well as an SCID I interview at the end of the study. Assessments regarding primary and secondary outcomes are carried out 10 times over the 12-month intervention period.

Methods to Achieve, Maintain, and Document Blindness of Assessments

The aripiprazole and CM as well as placebo and CM are provided double-blind with placebo identical to aripiprazole regarding packaging, appearance, color, and taste. Although blindness regarding the ''pill'' conditions is guaranteed by this procedure, in order to reduce rater bias in the CBT arm, where appropriate, self-ratings

are used as outcome measures (although validity of the findings [eg, depression/anxiety] might be reduced by this procedure). In addition, to achieve and maintain single blindness regarding the outcome measures transition to psychosis and most secondary outcomes, all conditions are carried out independently of the assessors who are kept unaware of treatment allocation (pill vs CBT). Extensive steps are taken to maintain the masking of the raters by methods successfully used in earlier studies.[56] Therapists and assessors are not be permitted to communicate details about individual clients to each other; separate offices and administrative procedures are provided for assessors and therapists; data storage and management are kept separate and secure; and clients are instructed not to disclose details of their treatment to assessors. Assessors are asked to record any loss of masking of treatment allocation regarding pill vs CBT. After a client completed the study, assessors are asked to guess the treatment allocation. At the end of the study, the success of the blinding procedure will be reported by the ratio of agreements between guesses of the treatment allocation by assessors and the real treatment allocation.

Quality Insurance and Monitoring of Treatment Fidelity

CM therapists are psychiatrists on registrar or consultant level who received a 1-day introductory workshop to the manual by the coordinating center at the commencement of the trial and a 3 hour workshop every 12 months since then.

CBT therapists are CBT-trained psychologists or psychiatrists who need to have at least 2 years experience in CBT. The coordinating center provided an intensive 3-day training workshop for therapists and a 1-day booster workshop every 12 months. Throughout the study, at least biweekly meetings are held at each center to discuss treatment fidelity and general patient management and supervision. In addition, expert supervision and conference calls with the study coordinator (A.B.) are used to maintain treatment quality.

To ensure and maintain the same standards of CBT and CM at all centers, the following procedures are used: If agreement of trial participants can be obtained, all CM and CBT sessions are audiotaped. We use a modified German version of the Cognitive Therapy Scale for Psychosis (CTS-PSY[57]) by Wittorf et al[58] to monitor the therapist's competence in CBT and to discriminate CBT from CM. The CTS-PSY consists of a general and a specific scale as well as a global judgment of the quality of the cognitive behavioral techniques used. The CTS-PSY demonstrated excellent interrater reliability and good validity[57] and has been successfully used in large-scale CBT trials in patients with psychosis.[59] Regular monitoring of audiotaped sessions by the coordinating center during the study and related training ensures high-quality CBT therapy and that no CBT is performed in the CM condition. At the end of the study, a random sample of audiotaped therapy sessions will be assessed by an independent rater blind to all site and participant data. The tapes selected will be stratified according to trial site, prevention strategy (CM and CBT), stage of individual therapy (early, middle, and late sessions), and time of entry to the study (early, middle, and late recruit). Rate of correctly classified tapes (CBT vs CM), mean CTS scores for CBT and CM, and significant differences between conditions will be reported for the overall sample and every trial site. In addition, performance of trial sites will be checked for significant differences to the overall sample.

Role of the Funding Source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the article.

Results

Enrolment and Subject Characteristics

Recruitment started in April 2008. Figure 1 illustrates the flow of subject selection until November 11, 2010. A total of 1650 help-seeking adults were screened. From those, 503 (30.5%) fulfilled the inclusion criteria. The main reason for not being eligible for randomization was present or past treatment with antipsychotics ($n = 139$) followed by having experienced a psychotic episode and substance dependence. Of those who were eligible for randomization ($n = 354$), 44.1% agreed to be randomized. No differences were found in gender ($\chi^2 = 0.173$, $P = .67$) and age distribution ($t = 0.077$, $P = .938$) between people who were eligible for randomization and agreed to be part of the RCT and those who did not agree. As regards source of referral (primary health care, mental health professional, counseling, and other), there were no differences between those who agreed to randomization and those who did not, except for those who were referred by a mental health professional: This population was significantly more likely to end up as refusers rather than participants ($\chi^2 = 7.838$; $P = .005$), most likely because they already established a therapeutic relationship with the referrer (table 2).

A description of the randomized sample is given in table 2. The mean age was 23 years, and the majority of participants were male. Only a minority of the participants were working or living with a partner. Almost 15% of the participants had a first-degree relative with a psychotic disorder. The intensity and frequency of positive and negative psychotic symptoms was relatively small as could be expected from a sample with subthreshold psychotic symptoms. The participants had moderate depression symptoms and were substantially compromised

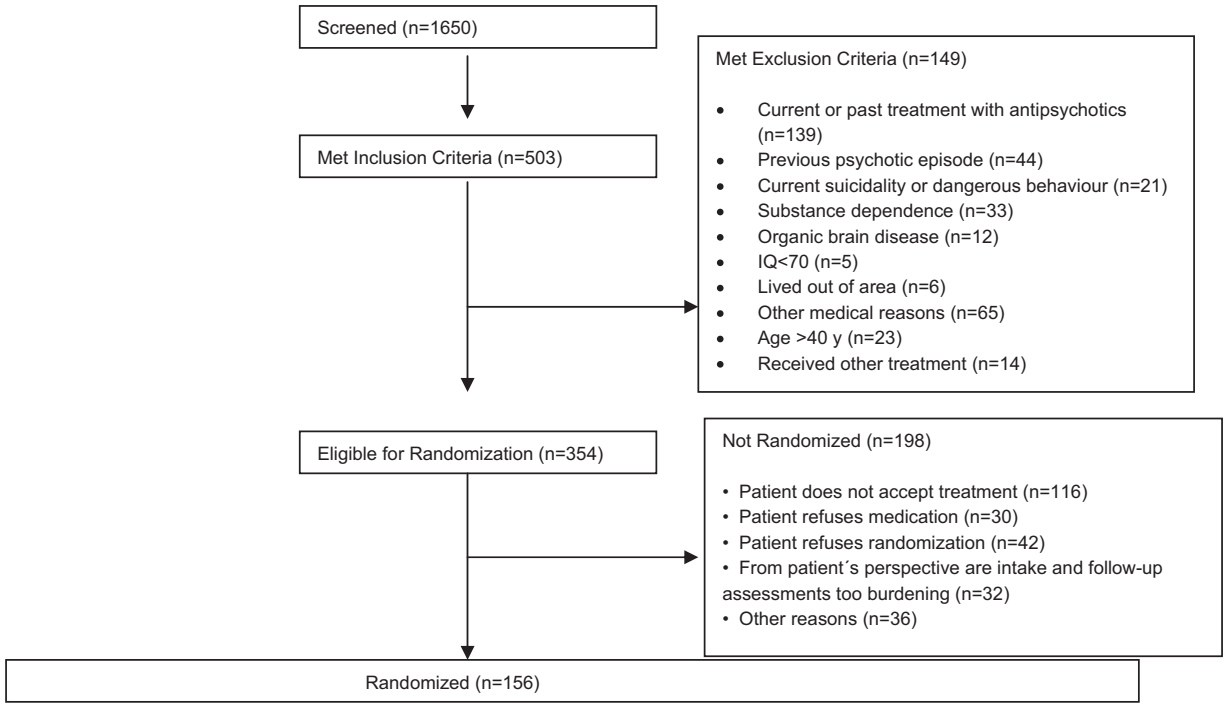

Fig. 1. CONSORT diagram.

at intake. The majority of the participants presented with attenuated psychotic symptoms at intake followed by BS.

DSM-IV Diagnostic Comorbitity

One hundred twenty-three (78.3%) of the randomized sample fulfilled criteria of a DSM-IV diagnosis (cf table 3). These diagnoses were mainly major depression, anxiety disorders, and substance use disorders. Out of the 149 participants who received an SCID II assessment, 68 (45.6%) fulfilled criteria for a personality disorder. The majority of clients who received an SCID II diagnosis received a Cluster C diagnosis followed by Cluster A. The most frequent diagnoses were avoidant personality disorder followed by paranoid personality disorder.

Preferred Preventive Intervention

By the time of randomization, participants were asked which condition they would prefer to be randomized to. The majority of the 171 participants prioritized CBT (51.5% $n = 88$), whereas 12.9% ($n = 22$) preferred pharmacological treatment, and 31.0% ($n = 53$) had no priorities.

Treatment Fidelity in CBT and CM

By November 2010, the audiotaped treatment sessions of 8 randomly selected clients randomized into CM and of 30 clients randomized into CBT were assessed with a modified version of the CTS-PSY[57] by Wittorf et al.[58] CBT-specific skills (means [SD]: 73.4 [10.8] vs 29.0 [12.2], $P < .001$) as well as general skills (means [SD]: 103.7 [9.2] vs 80.6 [10.6], $P < .001$) were scored as significantly higher in the CBT sessions than in the CM sessions. Thereby, the absence of CBT techniques in the CM group was confirmed. The quality of the CBT was rated as "good" as indicated by an "overall rating CBT interventions" of 23.5.

Discussion

To our knowledge, this is the first trial evaluating CBT as compared with antipsychotic treatment and CM combined as well as to placebo and CM combined.

The consort diagram indicates that in clinical practice—at least in Germany—antipsychotics are widely used in an at-risk population. One hundred thirty-nine (27.6%) out of 503 clients who met inclusion criteria could not enter the trial because they already received antipsychotic medication. This is noteworthy because, given the current state of the literature, prescribing antipsychotics is not evidence based in this population and is not covered financially by health insurances (cf "Introduction" section).

Compared with other RCTs in the at-risk population, the participation rate of 44.1% was substantially lower than in trials, which exclusively offered psychosocial interventions (95.2%,[13] 78.5%,[15] and 56.4%[14]) or omega-3-fatty acids (76.4%[17]) but corresponds to other trials, which evaluated antipsychotic treatment (43.7%[12]). Viewed together with the findings that by the time of randomization more than 50% of the participants preferred CBT while only 12% preferred

Table 2. Baseline Characteristics of the PREVENT Trial and of Completed Intervention Trials in People At-Risk of Psychosis

	PREVENT	McGorry et al[12]	Morrison et al[13]	McGlashan et al[16]	Amminger et al[17]	Addington et al[14]	Bechdolf et al[15]
Experimental condition	Aripiprazole + CM/CBT	CBT + low-dose risperidone	CBT	Olanzapine	Omega-3-fatty acids	CBT	Integrated Psychological Intervention
Control condition	Placebo + CM	Need-based intervention	Monitoring	Placebo	Placebo	SC	SC
Number of participants (*n*)	156	59	58	60	81	51	128
Age: mean (SD)	23.86 (4.89)	20 (4)	22 (4.5)	17.7 (4.75)	16.4 (2.05)	20.95 (4.12)	26 (5.8)
Gender *n* (%)							
Male	106 (67.94)	34 (58)	40 (69)	39 (64.9)	27 (33.3)	36 (70.6)	81 (63.25)
Female	50 (32.05)	25 (42)	18 (31)	21 (35.1)	54 (66.7)	15 (29.4)	47 (36.75)
Married, cohabiting with significant other *n* (%)	36 (28.8)	—	—	Married 2 (6.6)	—	4 (3.95)	52 (42.45)
Currently working *n* (%)	23 (19.5)	—	7 (12)	—	—	24 (23.55)	27 (21.05)
Family history of psychotic disorder *n* (%)	30 (13.4)	—	5 (8.6)	13 (21.95)	16 (19.7)	—	—
SIPS score mean (SD)							
Total	28.97 (11.3)	—	—	38.59 (14.46)	—	—	—
Positive	6.99 (3.89)	—	—	9.26 (4.3)	—	11.55 (4.55)	—
Negative	10.56 (5.6)	—	—	14.83 (7.06)	—	7.95 (5.2)	—
Disorganization	3.65 (2.3)	—	—	6.28 (3.67)	—	—	—
General	7.77 (3.4)	—	—	7.86 (4.02)	—	—	—
PANSS mean (SD)							
Total	46.11 (11.42)	BPRSP score	59.3 (9.9)	63.28 (16.72)	58.55 (13.5)	—	48.95 (4.33)
Positive	10.61 (2.96)	4.6 (2.6)	14.7 (3.1)	13.31 (3.52)	14.6 (3.25)	—	9.3 (2.5)
Negative	10.73 (4.38)	SANS score	13.05 (4.5)	17.21 (6.81)	13.85 (5.9)	—	11.15 (4.1)
General	24.77 (6.43)	19.5 (12.8)	31.6 (5.45)	32.76 (8.65)	30.15 (6.9)	—	28.5 (6.4)
Depression mean (SD)	MADRS 19.9 (7.4)	HRSD 19.9 (8.7)	—	MADRS 14.48 (7.94)	MADRS 18.2 (8.8)	CDSS 5 (4.65)	MADRS 19.1 (7.75)
Level of functioning at inclusion mean (SD)	SOFAS 52.46 (13.16)	GAF 61 (13)	GAF 48.65 (12.35)	GAF 41.9 (11.33)	GAF 60.5 (12.55)	GAF 58.85 (12.15)	GAF 59.35 (10.55)
Entry criteria *n* (%)							
BS-COPER	—	—	—	—	—	—	123 (96.1)
BS-COGDIS	86 (55.1)	—	—	—	—	—	—
APS	108 (69.2)	—	48 (82.75)	57 (95.0)	75 (92.5)	51 (100)	—
BLIPS	10 (6.4)	—	6 (10.3)	—	5 (6)	—	—
State and trait	25 (16.0)	—	4 (6.8)	13 (21.6)	6 (7.5)	—	35 (27.25)

Note: APS, attenuated positive symptoms; BLIPS, brief limited intermittent psychotic symptoms; BPRSP, Brief Psychiatric Rating Scale Psychotic Subscale; BS, basic symptoms; CDSS, The Calgary Depression Scale; CM, Clinical management; CBT, Cognitive Behavior Therapy; COGDIS, BS criterion cognitive disturbances; COPER, BS criterion cognitive-perceptive; GAF, Global Assessment of Functioning Scale; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, The Positive and Negative Syndrome Scale; SC, Supportive Counseling; SIPS, Structured Interview for Prodromal Syndromes; SOFAS, Social and Occupational Functioning Assessment Scale.

Table 3. DSM-IV Diagnostic Comorbidity

	(*N*; %)
SCID I diagnoses (*N* = 157)	
Adjustment disorders	7 (4.45)
Anxiety disorders	
Agoraphobia	2 (1.2)
Anxiety disorder substance induced	2 (1.2)
Obsessive-compulsive disorder	6 (3.8)
Panic disorder	10 (6.3)
Phobias	17 (10.8)
Social phobia	19 (12.1)
Posttraumatic stress disorder	4 (2.5)
Anxiety disorder nos	6 (3.8)
Eating disorders	
Bulimia nervosa	1 (0.6)
Binge eating	4 (2.5)
Mood disorders	
Dysthemic disorder	15 (9.55)
Major depression	61 (38.85)
Depression nos	3 (1.9)
Somatoform disorders	
Body dysmorphic disorder	2 (1.2)
Hypochondriasis disorder	1 (0.6)
Pain disorder	2 (1.2)
Somatization disorder	3 (1.9)
Unspecific somatoform disorder	1 (0.6)
Other DSM-IV Diagnosis	6 (3.8)
Substance abuse disorder	
Alcohol	15 (9.6)
Cannabis	21 (13.5)
Other	1 (1.57)
Proportion of *N* with at least one or more diagnoses	123 (78.3)
SCID II diagnoses (*N* = 149)	
Cluster A	
Paranoid personality disorder	13 (8.7)
Schizotypal personality disorder	6 (4)
Schizoid personality disorder	5 (3.3)
Cluster A total	24 (16.1)
Cluster B	
Antisocial personality disorder	4 (2.6)
Borderline personality disorder	6 (4)
Histrionic personality disorder	2 (1.3)
Narcissitic personality disorder	3 (2)
Cluster B total	15 (10)
Cluster C	
Avoidant personality disorder	31 (20.8)
Dependent personality disorder	3 (2)
Obsessive-compulsive personality disorder	9 (6)
Cluster C total	43 (28.9)
Other personality disorder	24.8 (16.6)
Personality disorder nos	7 (4.7)
Proportion of *N* with at least one or more diagnoses	68 (45.6)

Note: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; Structured Clinical Interview for Diagnostic and Statistical Manual IV Axis I Disorders, SCID I

pharmacological treatment, these data indicate that persons at-risk on average prefer interventions with minimal associated risks like psychosocial interventions or omega-3-fatty acids rather than antipsychotics in which the risk-benefit ratio is perceived as more controversial. This belief in people at-risk of developing first-episode psychosis is in line with those of the general population who prefer psychosocial interventions to pharmacological interventions too.[22,23]

The sample characteristics are comparable to those of earlier RCTs in the at-risk population. This statement applies particularly well to the gender ratio, current work situation, and family history. As in all other studies, the majority of participants were male, only one-fifth was in the work force and 15%–20% presented with a genetic risk of psychosis. Due to the fact that PREVENT is exclusively recruiting clients at the age of 18 or older, the mean age of the PREVENT population is higher than in studies which recruited adolescents as well.[12,16,17] This finding is consistent with the sample characteristics of earlier RCTs conducted by our group.[15,60] Because subtle, subjective, subclinical cognitive-perceptive disturbances (BS—COGDIS), which have not yet developed into attenuated or frank psychotic symptoms, served as inclusion criteria, the PREVENT sample showed lower positive symptom scores (PANSS) and attenuated positive scores (SOPS) than the samples of the other RCTs, which mainly recruited those with subthreshold psychosis (UHR criteria). An exception is the trial by Bechdolf et al,[15] which recruited clients presenting with BS (although from a different cluster) as well, and therefore psychosis and attenuated psychosis symptoms scores were low, too. With regard to depression, our baseline findings are consistent with the findings from the other cohorts indicating mild to moderate depressive syndromes in the respective at-risk cohorts. In contrast to the relatively low levels of symptom severity on measures like PANSS or MADRS, we found high levels of functional disability as reflected in Global Assessment of Functioning or SOFAS scores between 40 and 60 throughout all at-risk samples. Such a disjunction between symptom and functional severity is consistent with the findings in recent naturalistic samples.[9,10] As regards to entry criteria, in line with earlier trials, the main pathway into the trial was via the attenuated symptom group. Very few participants entered via the brief limited psychotic symptoms group. More than 50% fulfilled the BS criteria, which supplemented UHR criteria in the PREVENT trial.

As has been reported earlier for other at-risk samples, the PREVENT cohort showed substantial DSM-IV diagnostic comorbidity with axis I and II disorders. Our findings that 39% of participants had major depression, around 30% had anxiety disorders, and around 25% had substance use disorders (excluding substance dependence) are slightly lower than in the only other RCT in

which comorbidity was reported (41% major depression, 43% anxiety disorder, and 29% alcohol or cannabis abuse[14]). However, our numbers correspond to the ones reported for the North American Prodrome Longitudinal Study (NAPLS) cohort, the biggest at-risk cohort which has been examined in this respect so far. In this study, out of the 377 assessed patients, 69% had one or more mood/anxiety diagnoses and 25% had one or more substance abuse or dependence diagnoses,[61] which are similar to the numbers reported in earlier studies with smaller sample sizes.[62,63] As regards to axis II disorders, no other RCT reported the related comorbidity. However, the frequency of 45.6% of participants having at least one comorbid axis II disorder and the majority being Cluster C and Cluster A disorders in our sample again corresponds to the findings of the NAPLS study indicating an axis II comorbidity of 44%.[61]

Methodological Considerations

PREVENT is a methodologically sound trial, which will help to overcome some of the methodological shortcomings of earlier trials in people at-risks of developing first-episode psychosis. It will therefore add substantially to the empirical basis of interventions in the at-risk mental state. Methodological strengths are as follows: (a) systematic screening and detailed documentation of reasons for exclusion and nonparticipations of clients; (b) a sample size big enough to detect clinical relevant differences between trial conditions; (c) clear descriptions of the method used to assign treatment; (d) combining UHR and BS criteria, which, according to current knowledge, are associated with the highest and most reliable transition rates to psychosis[9,31]; (e) single- and double-blinded ratings with extensive monitoring and documentation of blindness; (f) highly manualized and standardized treatments, in which fidelity is frequently monitored and documented; (g) defining and assessing safety criteria (depression, suicidality, suicide, worsening of symptoms, and pharmacological side effects); and (h) the application of reliable and valid scales, which have been developed to assess at-risk symptoms, are applied (eg, SIPS/SOPS[4] and SPI-A[47]).

Clinical Consequences

The data presented indicate that the at-risk sample collected at the 9 centers across Germany showed clinical characteristics within the expected range. In summary, the sample characteristics of low global functioning and 78% axis I and 46% axis II comorbidity support the notion that treatment of the at-risk population is indicated both due to existing symptomatic and functional impairment and as indicated prevention.[64]

If the evidence endorses the research questions of the trial, indicated prevention will be empirically justified as a standard practice in mental health, suggesting that CBT and aripiprazole are equally effective for the prevention of psychosis. People at-risk will thus benefit from a choice of prevention strategies. Because psychotherapy of severe mental conditions, including psychosis, is more readily accepted and perceived as less stigmatizing than treatment with antipsychotics, including CBT as a prevention strategy may improve acceptance and tolerance of, and compliance with, indicated prevention efforts in persons at-risk in their families and in the general population. The inclusion of such treatments may therefore improve the impact of the mental health system on burden, disability, and economical consequences of schizophrenia.

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