The Clinical and Cost-effectiveness of a Self-management Intervention for Patients with Persistent Depressive Disorder and their Partners/caregivers: Study Protocol of a Multicenter Pragmatic Randomized Controlled Trial.

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Study protocol

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Abstract

Background*:* After regular treatment, patients with persistent depressive disorder (PDD) may remain in specialized psychiatric outpatient care without achieving remission. Lacking other options, these patients often receive long-term, non-protocolized care as usual (CAU) that does not involve the partner/caregiver of the patient. Although the revised depression treatment guidelines suggest focusing on psychiatric rehabilitation and self-management as the next treatment step for PDD, an evidence-based cost-effective self-management protocol for PDD is lacking. This study investigates the "Patient and Partner Education Program for All Chronic Illnesses" (PPEP4All) as a brief self-management protocol that could lead to lower costs, higher quality of life, and less disease burden in PDD patients and their partners/caregivers.

Methods*:* Presented is the rationale and methods of a multicenter pragmatic randomized controlled trial to evaluate the clinical efficacy and cost-effectiveness of PPEP4All for patients with PDD and their partners/caregivers. In accordance with current recommendations, a mixed-methods approach is used with both quantitative and qualitative data. A total of 178 eligible outpatients with PDD and their partners/caregivers are recruited and randomized to either PPEP4All or CAU. Those assigned to PPEP4All receive nine weekly self-management sessions with a trained PPEP4All-therapist. Primary and secondary outcome measurements are at 3, 6, 12 months.

Discussion*:* This project will result in the implementation of a self-management intervention for patients with PDD, meeting an urgent need in mental healthcare. Using PPEP4All can optimize the quality and efficiency of care for both patients with PDD and their partners/caregivers.

Trial registration: Netherlands Trial Register Identifier: NTR5973. Registered on 20 July 2016.

Background

Approximately 10–17% of persons with major depressive disorder (MDD) suffer a chronic course, or a continuous period of at least two years [1]. Two types of depressive disorders have a prolonged duration: chronic major depressive disorder and dysthymic disorder [2]. These were combined into one syndrome, persistent depressive disorder (PDD), in the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5). PDD has a 3–6% lifetime prevalence [3–7] and adverse consequences for patients when compared to less persistent forms of depression, such as impaired functioning in social and family relationships, high disease burden for both patient and partner/caregiver, reduced performance in work, comorbid psychiatric and somatic problems, and an increased suicide risk [8, 9].

Many patients with PDD remain in specialized outpatient care without achieving remission, even after having been treated according to the (inter-)national multidisciplinary depression guidelines [4, 10–12]. Clinicians are resigned to providing long-term supportive non-specific treatment due to the considerable suffering of patients and the absence of alternative treatment options [13]. More intensive prolonged care, however, often fails to improve therapeutic response; previous research has shown that patients with increasing depression symptom levels have a poor treatment prognosis despite receiving more

intensive care [14–16]. The ongoing unsuccessful treatment leaves both patients and clinicians feeling powerless and frustrated [13]. Moreover, this treatment often disregards the partner/caregiver of the patient, although involvement of the partner/caregiver has been shown to be beneficial in improving treatment results of the patient and reducing the partner's psychosocial burden concerning patient's disease [17–21].

The revised multidisciplinary guidelines for depression treatment [11, 22–27] advise focusing on psychiatric rehabilitation as the next therapeutic step for PDD patients with inadequate treatment results. Psychiatric rehabilitation using self-management interventions focuses less on symptom recovery and more on restoring psychosocial functioning and enhancing patient autonomy. Individuals with PDD learn to set realistic goals (e.g. regarding work reintegration) and to cope by adjusting their activities to compensate for restrictions caused by the chronic illness. To date, there is still an urgent need in specialized mental healthcare for a brief evidence-based, cost-effective treatment protocol concerning self-management for treatment-resisting persons with PDD that also involves the partner/caregiver and replaces long-term non-specific usual care.

This project evaluates the clinical- and cost-effectiveness of a self-management intervention in patients with PDD and their partners/caregivers, namely, the "Patient and Partner Education Program for All Chronic Illnesses" (PPEP4All). Additionally, we further our understanding of the healthcare needs for PDD and elicit direct feedback about PPEP4All from patients, partners/caregivers and clinicians via qualitative interviews. Compared to usual mental healthcare, we expect that PPEP4All will lead to an improved quality of life, fewer psychiatric symptoms, and more mental resilience in patients (using superiority testing). Moreover, we expect that PPEP4All will lead to lower psychosocial burden from the chronic disease for both patients and their partner/caregiver. Due to the anticipated higher effectiveness of the brief PPEP4All, we expect an additional reduction in societal and healthcare costs.

Methods

Study design

In this multicenter, pragmatic randomized controlled trial (RCT), the protocolized PPEP4All self-management intervention is evaluated against the care as usual (CAU) in specialized outpatient mental health care clinics in the Netherlands. Measurements are at 0 (pre-treatment), 3 (post-treatment), 6 (first follow-up), and 12 months (second follow-up), with assessors blind to randomization status. In accordance with current recommendations (in the context of RCTs) [28–33], we use a mixed-methods approach with both quantitative and qualitative data, wherein the qualitative study is nested in the main project. The qualitative data complements the quantitative data and can facilitate the practical implementation of the intervention, strengthen the clinical relevance of our results, and optimize the PPEP4All intervention by adding the perspectives of patients, partners/caregivers, and clinicians. Moreover, the study protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Additional file 1).

Setting and participants

Eligible patients are recruited from four large Dutch mental healthcare organizations, with 10 individual locations, that offer outpatient treatment for depressive disorders (see Acknowledgements). The primary research center of the study is the Department of Psychiatry of the Leiden University Medical Center (LUMC) together with GGZ Rivierduinen, a large mental healthcare provider in the Netherlands. The inclusion criteria for participating patients are as follows: a diagnosis of recurrent or chronic major depressive disorder (duration of at least two years) according to the DSM-IV [2] or PDD according to the DSM-5 [3]; age of 18 years or older; a treatment indication for rehabilitation as specified by the clinician, with a minimum of at least one already received psychological treatment and at least two medication trials according to the (inter)national multidisciplinary guidelines for depressive disorders [11,22–27]. Patients with recurrent or chronic depression who do not wish to complete all treatment steps of the depression guideline (e.g., refuse medication or electroconvulsive therapy) can also enroll in the study. Patients with bipolar disorder type II may also participate considering they generally spend much more time in a depressed state than in a hypomanic state, making it difficult to differentiate from recurrent depression [27, 28]. Bipolar disorder type I, however, was excluded. Further exclusion criteria for patients are: severe psychopathology such as a diagnosis of schizophrenia, current psychotic state, severe substance addiction, acute and severe risk of suicide; severe somatic disorders that are too disabling or render the patient immobile; severe cognitive problems such as dementia; and insufficient fluency in the Dutch language.

The inclusion criteria for partner/caregiver to participate in the self-management intervention are as follows: ability to participate in at least three sessions of the intervention and not currently receiving active psychotherapy.

Recruitment, enrollment, and allocation

Psychiatric nurses and psychiatrists of the participating mental healthcare locations identify patients eligible for participation according to the above inclusion and exclusion criteria, and they introduce research participation and provide information letters. Patients who are interested and consent to participate in the study sign an informed consent form, which is then sent to the primary research center (LUMC). On this informed consent form, participants can also indicate whether they want to be invited to a follow-up nested qualitative interview study in which we evaluate the satisfaction with PPEP4All and their coping strategies with chronic depression (see section Qualitative data).

To check the inclusion and exclusion criteria formally, a trained research assistant checks the DSM-IV depressive disorders with the Dutch translation of the Mini-International Neuropsychiatric Interview (MINI interview, modules A, B, and C regarding depression, dysthymia, and suicidality). The MINI interview is a well-validated semi-structured diagnostic interview used to identify psychiatric disorders, with excellent interrater and test-retest reliability [35,36].

Allocation of participants is performed by an independent data coordinator/data manager, who is not involved in data collection nor analysis (GC, see Acknowledgements). Participants are allocated to either PPEP4All or CAU, using a stratified randomization schedule (stratified by gender and research center) designed by an independent statistician of the Department of Medical Statistics and Bioinformatics of the LUMC.

For the patients allocated to PPEP4All, their main caregiver (e.g., partner, close family member, or close friend) is invited to participate in the project. The data manager makes an appointment with the partner/caregiver, and they sign an informed consent directly before the first measurement. Alternatively, the informed consent can be arranged by post prior to the first measurement. All participants are informed that participation is voluntary and that they can withdraw from the study at any time without consequences. Participants receive a 20-euro gift-card to thank them for their efforts. An overview of the study design and patient flow is provided in Figure 1.

Assessment and instruments

The measurement timepoints are at 0, 3, 6, and 12 months, of which the latter two are follow-up measurements. The first measurement is completed within one month prior to the start of the treatment. The study is conducted using a Routine Outcome Monitoring (ROM) system, which periodically measures the presence and severity of psychiatric symptoms in patients with a battery of psychometric instruments and thus monitors therapeutic progress [37–39]. To assist in the administration of the ROM measurements, a web-based application called QuestManager is available. At each timepoint, the questionnaires are completed online via QuestManager (see Figure 2 for the study schedule and overview of the questionnaires). If preferred or necessary (e.g., computer problems), questionnaires may be completed on paper. The participant may choose to complete the questionnaires at the location of their choice: at their home, the mental health clinic, the research center, or by telephone.

At the first measurement (i.e., 0 months), participant demographics are registered. At the second, third and fourth measurements (i.e., 3, 6 and 12 months), the primary and secondary outcome questionnaires are completed.

The primary outcome measures pertain to quality of life and healthcare costs. Quality of life is measured for both patients and partners/caregivers using the EuroQoL-5 (EQ-5D-5L, including the visual analogue scale, 5 items) [40–44]. Using the EQ-5D-5L, we calculate the quality-adjusted life-years (QALYs) gained, which is used in the cost-effectiveness analysis (CEA, see Economic evaluation). Healthcare consumption (such as contact with healthcare professionals, medical costs, and productivity loss) are measured with the Trimbos Medical Technology Assessment questionnaire for psychiatric illness-associated costs (TiC-P; 30 items) [45]. Symptoms, psychopathology, and well-being, for patients only, are measured using the Inventory of Depressive Symptomatology, Self-Report (IDS-SR; 30 items) [46–48]; the Symptom Questionnaire-48 (SQ-48; 48 items) [49–52]; and the Self-Rated Happiness survey (SRH; 1 item) [53–55], respectively. In addition, mental resilience of patients is measured using the Brief Resilience Scale (BRSnl;

6 items) [56,57]. The burden of the chronic disease for both the patient and partner/caregiver is measured by the Questionnaire on Burden of Chronic Disease for Patients (B4CZ; 20 items), and the Questionnaire on Burden of Chronic Disease for Partners (B4CZ partners; 16 items), respectively [58,59]. Directly after the final measurement, participants complete an additional qualitative survey pertaining to treatment modality, treatment satisfaction, number of therapy sessions, medication changes (yes or no), and PPEP4All treatment adherence.

Interventions

Self-management intervention (PPEP4All)

The self-management intervention called the “Patient and Partner Education Program for All Chronic Illnesses” (PPEP4All) was originally developed for chronic somatic diseases and then tested by EduPark, a research consortium with seven participating European countries [18,60–62]. Each of the PPEP4All sessions focuses on specific self-management themes, such as psychoeducation about chronic depression, stress-management using cognitive restructuring and relaxation techniques, reactivation via positive activity planning, social skills building, and mobilizing one’s social network. Although the original PPEP4All program had eight sessions, it has been suggested that an extra PPEP4All session may help sustain enhanced quality of life [19]. PPEP4All in this project includes a ninth session focusing on suicidality, dealing with crises, and relapse prevention. Regarding the latter, participants make a recovery or self-care action plan together with the PPEP4All-therapist, using the skills and information learned during the program. For an overview of the PPEP4All self-management themes, see Figure 3.

The partner/caregiver program (separate partner group) is the same as the patient program with only one difference: session five focuses on dealing with caregiver burden and patient suicidality (see Figure 3). The patient and partner/caregiver receive PPEP4All workbooks with homework assignments after each session to practice skills and integrate information. Although the original protocol describes a minimum of 5 and a maximum of 10 participants per group [17], we allowed groups to start with as few as 3-4 participants to avoid undue waiting times.

The PPEP4All program is eclectic, including theoretical influences of system theory (“patient system”) [63,64], cognitive behavioral theory (“(dys)functional cognitions”) [65], social cognitive theory (“self-efficacy”) [66], stress-coping model (“coping strategies”) [67,68], transtheoretical model (“motivation to change”) [69]; bio-psycho-social model (quality of life) [70–72], and generic model of self-management [73].

The clinical efficacy of PPEP4All has previously been established in patients with chronic somatic disorders, such as Parkinson’s disease, Huntington’s disease, and chronic pituitary disorders [17–19,74–77]. Research has shown that PPEP4All is effective: patients with Parkinson’s disease showed a significant improvement in quality of life after completion of PPEP4All [19]. Moreover, patients with

symptom-manifested Huntington's disease showed a significant improvement in active coping and social support-seeking and reported fewer behavioral problems and less anxiety. After six months, they also showed an improvement in psychosocial burden related to the chronic illness [75]. Patients with chronic pituitary disorders showed significant higher self-efficacy after following PPEP4All [77]. Patients with chronic somatic illness often also experience long-term anxiety and depression. After following PPEP4All, patients with various chronic somatic disorders and comorbid chronic depression showed an improvement in depression scores [18]; an indication that PPEP4All could also be applied to mental healthcare as in the present study.

PPEP4All has particular advantages. First, this program involves and engages the partner/caregiver in the treatment process, which has been shown to be effective in reducing the partners' psychosocial burden concerning the patients' illness as well as the patients' outcome [17–21]. A key feature of PPEP4All is that the patient and partner/caregiver receive separate sessions. Maintaining separate sessions allows both patient and partner/caregiver to speak freely about their personal situations. Second, the program can be offered as a group or individual intervention. The treatment modality is determined by the patient and his or her therapist in a process of shared decision making. Third, patients with depression often have comorbid psychiatric or somatic disorders [14,78]; the PPEP4All program provides a general toolkit with which all these issues can be addressed. Fourth, each session of the program is structured, providing clarity to the form of the treatment. Patients and partner/caregivers work according to a PPEP4All workbook.

The clinicians of the participating mental health clinics who administer the program are called PPEP4All-therapists. Each therapist receives a treatment manual and completes a three-day certified course with the PPEP4All founder [17,18,79–82]. The training combines homework/self-study with lectures, assignments, group discussions, role play, and self-assessment. The 34 PPEP4All-therapists in this project are mainly psychiatric nurses or psychiatric nurse specialists and three are psychologists. After completing their PPEP4All training, all PPEP4All-therapists in this study could receive continuous support with regular booster sessions, intervision, consultation with the PPEP4All founder, and are invited for an annual national PPEP4ALL symposium.

Care as usual (CAU)

The participants randomized to the control group receive care as usual (CAU). This standard treatment for patients with PDD concerns mostly long-term, non-protocolized supportive care from a psychiatric nurse, with pharmacological maintenance therapy from a psychiatrist. CAU often has an individual treatment modality and does not usually include the partner/caregiver of the patient. Patients allocated to CAU in this study generally continue the standard treatment with their own therapist.

Treatment integrity

To evaluate the treatment integrity of PPEP4All, each PPEP4All-therapist completes a therapy protocol checklist at the end of each group or individual session. On this protocol checklist, the PPEP4All-therapist can indicate whether and how the provided treatment deviated from the treatment protocol (e.g., the themes mentioned in Figure 3). Attendance of participants is recorded on a separate attendance list and provided to the researchers by the PPEP4All-therapist. For CAU, without a specific treatment protocol, we cannot assess its treatment integrity. However, after the final fourth measurement, we collect information about treatment type and modality within CAU, including treatment satisfaction and general medication changes during the course of the research project.

Sample size and power calculation

We based our sample size on the effect size of previously conducted randomized controlled trials that evaluated relevant interventions in a similar setting in patients with chronic or treatment-resistant depression and that reported a quality of life outcome measure [83–87]. We can expect an effect size around 0.35 [85]. Considering a power level of 80% and alpha of 95%, we would require 81 participants per group [88–92]. With an additional 16 persons to account for an expected attrition of 10% [93], we expect to include a total sample of 178 participants.

Statistical analyses

In this project, we will examine both quantitative and qualitative data.

Quantitative data

Using the data collected from the questionnaires, we will examine the clinical and economic effectiveness of PPEP4All (in collaboration with the LUMC Department of Medical Decision Making). This is further specified below.

Clinical effectiveness

Quality-adjusted life-years (QALYs) will be estimated using EQ-5D-5L data from four assessments. For the primary data analysis, we will perform an analysis of covariance for the QALY's using the post-test EQ-5D-5L results with the pre-test scores as covariate [89–91]. In this way, we test whether there is a difference between PPEP4All and CAU, accounting for the variation where the patients started at the first measurement. For the secondary data analyses, secondary parameters will be tested using weighted generalized estimating equation (GEE) analyses [94,95]. Clinical effectiveness analyses will be examined using superiority testing.

Moreover, we will examine tailored care by further investigating for which groups PPEP4All is the most effective. If possible, subgroup analyses will be performed for age, gender, ethnicity, and intervention modality (group/individual). In this context, we will also explore relevant socio-demographics (e.g. education, living situation, and work) and clinical variables (e.g. comorbidity, baseline severity of disease).

For all outcome analyses, an intention-to-treat (ITT) approach will be used, according to the CONSORT statement [96]. Analyses will be conducted in SPSS, Stata or R.

Economic evaluation

We will perform two economic evaluation analyses (see below). The first is a cost-effectiveness analysis (CEA) to determine whether PPEP4All (compared to CAU) is favorably cost-effective at one-year follow-up. The second is a Budget Impact Analysis (BIA). The economic evaluation is based on the TiC-P questionnaire (see Figure 2). The TiC-P questionnaire assesses healthcare utilization such as general practitioner (GP) visits and non-healthcare use such as absence from work, reduced efficiency at work, difficulties with job performance (absenteeism from paid work), and production losses without absenteeism from paid work (e.g. presenteeism). Using the area-under-the-curve method for the utility scores will result in QALY outcome per patient.

Cost-effectiveness analysis (CEA).

Direct costs per patient in PPEP4All versus the costs per patient in CAU are compared. The differences in mean costs and effects between strategies will be compared with two-sided bootstrapping. In a net-benefit analysis, costs will be related to patient-reported outcomes and presented in a cost-effectiveness acceptability curve (CEAC), which indicates the probability of PPEP4All being cost-effective. No discounting will be applied considering the time horizon of one year. This economic evaluation will be approached from a societal perspective and includes costs due to healthcare resource utilization (i.e. healthcare costs) and costs attributable to production loses [97]. Sensitivity analysis will test whether estimates are sensitive to plausible changes in perspectives (societal or healthcare perspective) and indirect costs (friction cost method and human capital approach). Furthermore, in an additional analysis, we will extrapolate cost and effect estimates to a lifetime time horizon, in accordance with the recent Dutch directive for conducting economic evaluations in healthcare [98,99]. In the base-case analysis, costs of absenteeism from paid work is calculated using the friction cost method, which estimates the indirect costs of disease, mainly occurring during the time it takes to replace a worker [100–103].

In this project, costs are calculated using standard unit prices published in the most recent Dutch Costing Manual (2015) [98,99]. If references are not available, costs are estimated by cost research experts (i.e. LUMC Department of Medical Decision Making). The costs will be divided into healthcare costs, costs of patients and partner/caregiver, and costs in other sectors (i.e. non-healthcare costs such as productivity

costs). Healthcare costs include the costs of PPEP4All and other healthcare use during the first year of follow-up (e.g., GP visits, outpatient visits, hospital days, medication, home care, informal care). Costs of PPEP4All are based on micro-costing including time of caregivers and materials used. Costs of patients and partners/caregivers consist of time lost or productivity loss from paid and unpaid work of the patient, and time required for the PPEP4All meetings by partners/care givers.

Budget impact analysis (BIA).

In addition to the CEA, a BIA is performed according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force principles [104,105]. The BIA estimates the financial impact of implementation (i.e., adoption and diffusion) of PPEP4All in patients with PDD at the national level. The analysis is based on the costs estimated during the study and the expected number of patients eligible for this treatment in the Netherlands. Costs of the treatment and other consequences of it will be included in the BIA. The BIA is conducted from the perspective of the different healthcare payers (public purse or budgetary framework [in Dutch: Budgetair Kader Zorg (BKZ)]; health insurers; health care providers) and from the societal perspective (i.e., including productivity costs). If the PPEP4All intervention appears to be cost-effective in patients with PDD, the following scenarios will be compared: a) intervention not yet implemented, b) intervention implemented in 100% of the target group, c) intervention gradually introduced over a period of three years. Sensitivity analysis is performed on the costs of the intervention and the diffusion rate. Factors that determine the budget impact are determined. Costs are estimated per budget period (1 year) for a time horizon of 3 years. In the societal perspective and healthcare perspective, standard prices will be used [98]. For the BKZ and health insurer's perspective, tariffs established by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit (NZA)) are used.

Qualitative data

All patients and partners/caregivers who give consent to be approached for the nested follow-up qualitative study are invited by telephone to participate. The participant may choose where the in-depth semi-structured interview is planned: at the participant's home or at the main research location (LUMC). Interviews can also take place via telephone. Participants are compensated for travel and given a 20-euro gift card to thank them for their time. Participants are allowed to withdraw at any moment of the qualitative study.

For each interview, we use topic lists or interview guides (see Supplementary Topic Lists in Additional Files 2 and 3), which were initially evaluated in a pilot study of patients with PDD and revised as necessary [106,107]. The topics and questions are presented to the participant as they naturally arise during the interview, to maintain the flow of the interview. The qualitative study includes two parts that examined: a) coping strategies of PDD patients and their partners/caregivers with the chronic depression and their specific needs for care, and b) satisfaction of patients, partners/caregivers, and therapists with

PPEP4All (or CAU). The two parts are discussed in further detail below (see Coping with Depression and Satisfaction).

The interviews are recorded using a digital audio recorder and then transcribed by research assistants using the dictation feature of the online Transcribe application (https://transcribe.wreally.com). This application does not store documents; audio files are deleted after the window is closed, making it a secure method that maintains confidentiality after transcription work. Personal data that can be traced back to the participant (e.g., names of participant, family members, or employer) are removed, and transcripts are saved under a participant code. The verified transcripts are then checked and analyzed by the researcher (ES). Each interview and the resulting themes are discussed with the research assistants and tracked using an audit trail. Memo writing is utilized throughout the analytic process. Participants will be interviewed until saturation of the super-ordinate themes is achieved. Data are analyzed using Grounded Theory [108,109], with a constant comparative analysis method using Atlas.ti version 8 software. With constant comparison, we use a method that continuously compares the concepts or themes between interviews [110].

Coping with chronic depression

First, we aim to answer the following research questions: how do individuals with chronic depression manage their chronic condition, and what are their experiences in relation to potential facilitators and barriers,

personal strengths and hindrances, and self-management coping strategies? (see Supplementary Topic List A, or Additional File 2, which is partly based on a previous relevant topic list [107]). For this part of the qualitative study, we aim to include between 25 to 40 patients from the PPEP4All or CAU groups and 15 PPEP4All partners/caregivers to reach saturation of the themes [111–113].

Satisfaction

Second, we aim to evaluate satisfaction with PPEP4All and investigate how we can optimize it to meet the needs of the patients with PDD and their partners/caregivers. Our approach is multi-faceted: we conduct in-depth interviews with patients, partners/caregivers, and PPEP4All-therapists (see Supplementary Topic List B, or Additional File 3, which is partly based on the Mental Healthcare Thermometer [106]), and we collect data via an evaluation questionnaire at the end of the fourth quantitative measurement to elucidate the positive and negative aspects of PPEP4All. During the interview, the participants may provide feedback and suggestions regarding PPEP4All, and they rate the PPEP4All program on a scale from 1 to 10. We will provide the average rating for each group. This satisfaction rating reflects an indirect measurement of the effectiveness of PPEP4All. For this part of the qualitative study, we aim to include between 25 PPEP4All patients, 15 PPEP4All partners/caregivers, and

10 PPEP4All-therapists [111–113]. In addition, we strive to measure satisfaction with CAU, as a comparison with PPEP4All.

Ethics, data management, and dissemination

The study protocol, informed consent forms, participant education and recruitment materials were approved by the Medical Ethics Committee (MEC) of the LUMC. If there are any subsequent modifications to the protocol which may impact the conduct of the study, including changes of study objectives, patient population, sample sizes, study procedures or significant administrative aspects, these will be submitted as an amendment and reviewed by the MEC of the LUMC for approval. Subsequent to initial review and approval, the MEC will review the protocol annually and the researcher will make safety and progress reports to the MEC annually and within three months of study termination. These reports will include the total number of participants enrolled and any particularities that should be reported to the MEC. Due to the low risk associated with study participation, annual audit of the study and data monitoring committee are not required. Additionally, a data safety monitoring board is not required because we do not investigate a medical product and we do not foresee any major risks associated with study participation or with participation in the intervention provided and guided by trained therapists.

Written informed consent will be obtained from all participants prior to the baseline assessment. All informed consent forms will be arranged and co-signed by the researcher or trained research assistant who provided information regarding the study. For the nested qualitative study, each participant gave written consent to be approached for participation in this additional study. Participants thereafter gave verbal consent to the study including consent to audio recording and transcribe their interviews.

In general, we followed the guidelines for Good Research Practice (GRP) [114–117]. To protect the confidentiality of data and privacy of patients, we use a unique research code for each participant on all research-related participant forms, such as contact forms or paper questionnaires. This enables the research team to identify individuals without using names. The list linking the participant code to personal information is kept in a secure electronic database with access limited to the designated researcher (ES) and independent data coordinator (GC). The list may be assessed and the main mental health clinician of the patient informed if required for the sake of the safety of the participant. All electronic research-related participant information is stored on a protected network in a secure file with limited access. The hardcopy paper research information is kept in a locked cabinet in a secure area of the LUMC department. Any documents with information traceable to the participant are kept in locked files separate from the patient data with limited access. To uphold high standards of research, all researchers, research coordinators, and research assistants successfully completed the research certification for Good Research Practice (GRP). Additionally, all research team members completed a training workshop regarding the trial procedures and questionnaires, use of QuestManager, and administration of the MINI screening interview.

Moreover, after the data analysis phase, patient privacy will be further maintained. The results obtained from the questionnaires will be described on a group level to prevent the data being traced back to a single person. Data will be kept on the secure network for maximum three months at the end of the research project as the embargo period, for the sole purpose of completing data analysis, as per the policy of the funding sponsor. Once the final report of the study is available, the study results will be extensively disseminated to the international scientific community in the form of peer-reviewed journal articles, giving preference to open-access journals.

After the embargo period, the pseudonymized data will be stored for 15 years on an online meta-data catalogue called the Data Archiving and Networked Services (DANS, www.dans.knaw.nl) together with a data-dictionary, as is common practice for mental healthcare research in the Netherlands. Only the designated researchers will have access to the final data set. External researchers may get access to the final trial dataset from the designated team on reasonable request.

Discussion

Scientific and clinical importance of this study

The present study examines the clinical- and cost-effectiveness of a brief self-management intervention, namely PPEP4All, in patients with PDD and their partners/caregivers. Although self-management is more common in the treatment of somatic illnesses, it is gaining popularity in mental healthcare. Psychiatric rehabilitation via self-management is the next step in the revised (inter-)national multidisciplinary treatment guidelines for depression after (combination) psychotherapy and pharmacotherapy have been attempted with inadequate results. In this context, there is an urgent need in mental healthcare for a brief specific self-management protocol that could replace the long-term non-specific care for patients with PDD.

In the course of this project, other interventions have surfaced, such as the Wellness Recovery Action Plan (WRAP; a self-designed prevention and wellness process, mainly used for severe mental illness) [118,119]; Illness Management and Recovery (IMR; a standardized psychosocial intervention for severe mental illness like schizophrenia) [120]; and Self-management for Chronic Anxiety and Depression (SemCAD; for chronic depressive and anxiety disorders) [86,87,121]. PPEP4All has advantages when compared to these other interventions. First, we can apply this general self-management intervention to different chronic psychiatric illnesses, including PDD, and comorbid chronic somatic illnesses. Second, PPEP4All has a flexible treatment modality: although a group-oriented intervention is expected to be the most cost-effective for mental healthcare clinics, some patients may prefer the individual treatment modality. Third, PPEP4All involves partners or other caregivers. Partners/caregivers often provide the most care to the patient, and they experience long-term strain across all stages of the patient's illness, including the patient's suicidal thoughts and attempts. Therefore, attention for the caring capacity of the partner/caregiver in the treatment of a patient is crucial, because the partner's well-being directly influences the stability and health of the patient with depression [17–19].

Study implications

The findings of this study will have potential implications for the implementation of self-management on a national level in the Netherlands and could be further incorporated into the (inter-)national multidisciplinary treatment guidelines for depression. In the last years, the Netherlands has seen a shift in the organization of the mental healthcare system due to tighter healthcare budgets. Thus, mental healthcare clinics are looking for empirically-supported protocolized treatments that can reduce healthcare costs. With this in mind, PPEP4All is a brief self-management intervention that can be provided when depression treatment leads to unsatisfactory reduction of symptoms, typically after a two-year treatment period. The expectation is that empowering patients via PPEP4All will decrease the number of ongoing supportive sessions of CAU, for which there is little to no empirical evidence [13].

The present study has several strengths. First, in line with the pragmatic nature of the project, we focus on external validity: we evaluate the standard care (CAU) already provided by healthcare professionals in multiple mental healthcare clinics. Moreover, the broad inclusion criteria allow the recruitment of patients with a wide range of comorbidity, as typically seen with persons with chronic or recurrent depression. We expect the resulting sample to be broadly representative of outpatients and generalizable to the population of persons with chronic depression. We selected only the most crucial questionnaires for the measurements to limit the burden on the patients; therefore, we expect limited effect of the measurements on patient drop-out. Additionally, by using a mixed-methods approach, we are able to evaluate both quantitative and qualitative aspects of PPEP4All from multiple perspectives (patient, partner/caregiver, clinician).

Challenges concerning trial recruitment and implementation

We wish to report some early challenges we faced in the recruitment of participants and implementation of our study design and PPEP4All in the participating research centers. After all, there is a universal recognition that patient recruitment is a key determinant of success or failure for clinical trials [122, 123,124].

Firstly, we learned that recruiting only patients with a primary diagnosis of chronic depression/PDD limited our ability to also recruit potential participants with secondary, or comorbid, PDD (e.g., bipolar disorder type II participants with comorbid PDD). After deliberating, we also allowed these participants to enroll in our study considering that PPEP4All is a generic self-management program that could potentially be used for a wide range of psychiatric disorders and its focus is on recovery, stabilization, and reintegration into the community [125].

Secondly, we had to make the following adjustments for the convenience of participants [90]. Initially, we had proposed providing PPEP4All as group treatment, because a group could be the most cost-effective and efficient modality for mental healthcare. However, several patients with PDD preferred individual PPEP4All and therefore refused to participate. This possible preference for individual PPEP4All was also

reported to us by the Client Council of participating centers. For this reason, PPEP4All is now offered as a group or individual treatment. In addition, for patients with a preference for group PPEP4All, we lowered the minimum threshold of required group participants to three rather than the original five, which allowed us to start PPEP4All groups without a long waiting period. Also, some patients who explicitly wanted PPEP4All withdrew their study participation after they were randomized to CAU. We have remedied this with the message that, if necessary, these patients could receive PPEP4All after CAU and completing their (first or second) follow-up.

Conclusion

This self-management intervention, PPEP4All, could fill an urgent need in mental healthcare and provide further support for the use of psychiatric rehabilitation via self-management for patients with PDD and their partner/caregiver. Using psychiatric rehabilitation as the next step in the treatment guideline for PDD without remission could replace the non-protocolized usual care and optimize the quality and efficiency of depression care. The self-management intervention is expected to reduce costs for the mental health organizations and empower patients to achieve a higher quality of life.

Abbreviations

B4CZ: Questionnaire on Burden of Chronic Disease, version for Patients or Partners; BIA: Budget Impact Analysis; BRSnl: Brief Resilience Scale-Dutch translation, 6 items; CAU: care as usual; CEA: cost-effectiveness analysis; CEAC: cost-effectiveness acceptability curve; DANS: Data Archiving and Networked Services; DSM: Diagnostic and Statistical Manual of Mental Disorders; EQ-5D-5L: EuroQoL-5, including the visual analogue scale, 5 items; GEE: generalized estimating equation; GRP: Good Research Practice research certification; IDS-SR: Inventory of Depressive Symptomatology, Self-Report, 30-items; IMR: Illness Management and Recovery; ISPOR: International Society for Pharmacoeconomics and Outcomes Research-Task Force principles; LUMC: Leiden University Medical Center; MDD: Major depressive disorder; MINI: Mini-International Neuropsychiatric Interview-Dutch translation; NZA: Dutch Healthcare Authority (Nederlandse Zorgautoriteit); PDD: persistent depressive disorder; PPEP4All: “Patient and Partner Education Program for All Chronic Illnesses” self-management program; QALYs: quality-adjusted life-years; ROM: Routine Outcome Monitoring; SemCAD: Self-management for Chronic Anxiety and Depression; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SQ-48: Symptom Questionnaire-48, 48 items SRH: Self-Rated Happiness survey, 1 item; TiC-P: Trimbos Medical Technology Assessment questionnaire for psychiatric illness-associated costs, 30 items; WRAP: Wellness Recovery Action Plan.

Declarations

Trial Status

This trial is currently recruiting patients, which started on 1 April 2017 and is anticipated to end on 1 April 2021. The protocol is Version 5 dated 8 August 2019.

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Authors' contributions

IC conceived and developed the study design and coordinates the study. ES is conducting this study in fulfillment of a doctoral degree and was able to contribute to the study design. NvdW is involved in the oversight of the data collection. AvH is the department head and departmental responsible person. ES will perform the data analysis. ES drafted the manuscript and IC, NvdW, and AvH critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Datasets generated and/or analyzed during the current study will be pseudonymized and stored on an online meta-data catalogue called the Data Archiving and networked Services (DANS, www.dans.knaw.nl), according to the funding sponsor policy, with access limited to a designated team within the Department of Psychiatry of the Leiden University Medical Center. External researchers may get access to the final trial dataset from the designated team on reasonable request. The (intellectual) property rights with regard to the generated data will reside at the Leiden University Medical Center. Anonymized results will be published in peer-reviewed journals and presented in international conferences.

Ethics approval and consent to participate

This study protocol has been approved by the Medical Ethics Committee of the Leiden University Medical Center. All participants in the study will provide documented informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

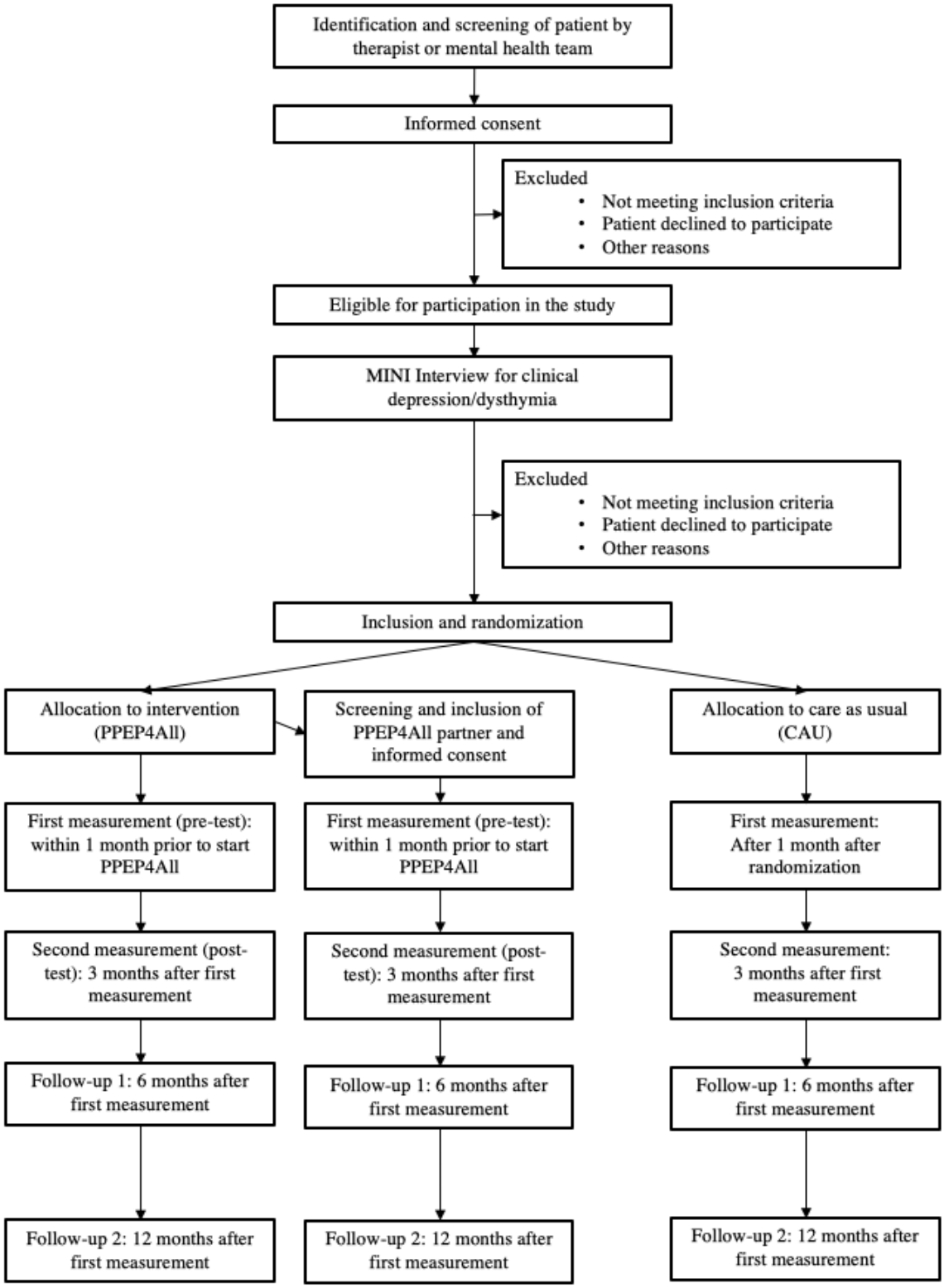

Figure 1

Study design and flow. Notes: MINI = Mini-International Neuropsychiatric Interview. PPEP4All = Patient and Partner Education Program for All Chronic Illnesses. CAU = care as usual.

	STUDY PERIOD					
	Enroll-ment	Allo-cation	Post-Allocation		Follow-Up	
TIMEPOINTS	$-t_1$	0	t_1 0 mo.	t_2 3 mo.	t_3 6 mo.	t_4 12 mo.
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
PPEP4All (intervention group)			⟷	⟷		
Care as usual (control group)			⟷	⟷		
ASSESSMENTS:						
Clinical depression/suicidality (MINI, modules A, B, and C)	X					
Demographics*			X			
Quality of life (EQ-5D-5L)*			X	X	X	X
Healthcare costs (TiC-P)			X	X	X	X
(Residual) depressive symptoms (IDS-SR)			X	X	X	X
Psychopathology (SQ-48)			X	X	X	X
Happiness (SRH)			X	X	X	X
Mental resilience (BRSnl)			X	X	X	X
Patient burden of living with chronic disease (B4CZ)			X	X	X	X
Partner burden of living with chronic disease (B4CZ-partners)*			X	X	X	X
Questionnaire regarding treatment integrity (therapists) and satisfaction						X

Figure 2

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule of enrollment, interventions, and assessment of the study. Notes: MINI = Mini-International Neuropsychiatric Interview [35-36]. EQ-5D-5L = EuroQoL-5 with visual analogue scale [40-44]. TiC-P = Trimbos Medical Technology Assessment questionnaire for psychiatric illness-associated costs [45]. IDS-SR = Inventory of Depressive Symptomatology, self-rated [46-48]. SQ-48 = Symptom Questionnaire-48 [49-52]. SRH = self-rated

happiness [53-55]. BRSnl = Brief Resilience Scale [56-57]. B4CZ = Questionnaire on Burden of Chronic Disease for Patients (or Partners) [58-59]. * denotes the questionnaire that are administered to partners/caregivers in the study.

Session 0	Session 1	Session 2	Session 3	Session 4
Intake Discuss burden and care needs. Provide workbook.	**Introduction** Discuss group rules and create safe space. Set personal goals.	**Self-evaluation** Gain insight into patterns of emotions, thoughts, and events by keeping a diary.	**Health promotion & relaxation** Discuss emotions, thoughts. Plan positive activities (activation).	**Stress-management** Coping with stress using cognitive restructuring or body scan and meditation.
Session 5	**Session 6**	**Session 7**	**Session 8**	**Session 9**
Psycho-education Learning more about chronic depression, comorbidity.[a]	**Social skills & competence** Building social skills.	**Increasing social support** Defining one's social and help network.	**Suicide prevention & relapse plan** Making a recovery or crisis plan based on skills learned.[b]	**Review & moving forward** Check progress, review goals, exchange personal cards.

Figure 3

An overview of the self-management themes per PPEP4All session for the patient and the partner/caregiver. Notes: PPEP4All = Patient and Partner Education Program for All Chronic Illnesses. Patient and partner/caregiver programs include the same themes with the exception of session 5 and 8. Each session has a general structure of discussing previous homework, presenting active information (i.e., the theme), performing an active exercise, then providing homework and a preview of the next session. Trainer is PPEP4All-therapist. a In partner/caregiver program, session 5 focuses on caregiver burden and stress. b In partner/caregiver program, session 8 focuses on making a self-care plan.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additional1.SPIRITChecklist.doc
- Additional2.TopiclistA.docx
- Additional3.TopiclistB.docx