COGNITIVE-BEHAVIORAL TREATMENT OF DEPRESSION IN PATIENTS WITH ACUTE CORONARY SYNDROME (TREATED ACS Study)

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Multicentre research grant application form

GENERAL INFORMATION

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1.Title	COGNITIVE-BEHAVIORAL **TREATME**NT OF **D**EPRESSION IN PATIENTS WITH **A**CUTE **C**ORONARY **S**YNDROME	
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3. Partners and Centres involved in the study (Max. 5)		
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Consortium Agreement	YES X	NO

4. Previous support by the Compagnia di San Paolo		
Previous Support by the Compagnia di San Paolo to the Coordinator and/or the Investigators?	YES	NO X
If YES, provide details (Grant holder, project title and duration, amount funded)		

5. Abstract

The abstract (Max. 250 words) should be organized in the following sections: (i) State of the art; (ii) Objective and rationale; (iii) Experimental Plan; (iv) Expected results and their relevance.

State of the art: Depression in association with acute coronary syndromes (ACS) is an independent risk factor for subsequent cardiac events and mortality. However, the only randomised behavioral intervention trial attempting to reduce cardiac risk in depressed ACS patients showed that changes in depression did not translate into improved survival. Such intervention did not address issues such as lifestyle modification and improvement in psychological well-being, which were found to affect individual vulnerability to medical disease. Our research group has developed a well-being enhancing psychotherapeutic strategy, well-being therapy (WBT), which has been validated in a number of controlled clinical trials.

Objective and rationale: To evaluate the efficacy of cognitive behavioral treatment (CBT) with WBT in improving depressive symptomatology and well-being, as well as reducing cardiac risk in depressed and/or demoralized ACS patients compared to clinical management (CM). The same protocol will be carried out in two centres (Bologna and Torino).

Experimental plan: 100 patients after a first episode of ACS, meeting DSM-IV criteria for depressive disorders and DCPR criteria for demoralization will be randomized to one of two treatment groups: 1) CBT supplemented by WBT; 2) CM. In both groups, treatment will consist of twelve, 45-minute sessions once a week. A two-year follow-up will be performed.

Expected results and their relevance: It is expected that psychological treatment may significantly decrease psychological distress, cardiac morbidity and mortality at follow-up compared to clinical management. The findings may entail considerable preventive implications and possible large reductions in health costs.

RESEARCH PLAN

Background and rationale

Cardiovascular diseases are the leading cause of death and disability in Europe. Acute coronary syndromes (ACS), such as myocardial infarction and unstable angina, are comorbid with major depressive disorder (APA, 2000) almost 20% of the time. Depression is more than transitory psychological distress: the period of sadness or lack

of interest is abnormally intense or abnormally long and interferes with a variety of personal, interpersonal and social activities. Most patients with depression during the initial ACS hospitalization continue to have depression 1 to 4 months later. Depression impairs health status more than heart disease itself and it is also associated with poor long-term psychosocial outcomes. Several studies suggest that major depressive disorder, and minor depression, that do not meet the criteria for a diagnosis of major depressive disorder, in addition to their effects on quality of life, are risk factors for recurrent events in patients with established cardiac disease (Barth et al, 2004; Rafanelli et al, 2006, 2007). Several prognostic studies have shown that depression is a predictor for survival after ACS (Frasure-Smith et al, 1995) independently of previous cardiac history, cardiac disease severity, or residual left ventricular function. The risk is directly related to the severity of mood symptoms: a 1- to 2-fold increase in ACS for minor depression and a 3- to 5-fold increase for major depression (Bunker et al, 2003; Carney et al, 2008).

Recent studies remark that the classification into diagnostic subgroups of affective disorders is important for an improved clinical and pathophysiological understanding of the relationship with cardiovascular diseases. Dysthymia, a chronic feeling of depression, less intense than major depression, plays an important role regarding this relation. Moreover, dysthymia has shown a stronger association with ACS than unipolar major depression (Baune et al, 2006). In an article by Rafanelli et al (2010), the authors found a prevalence of 13.4% of dysthymia in CHD patients. Among the variables examined as potential risk factors for cardiac outcome events, only dysthymia diagnosis in the years preceding the first episode of CHD attained statistical significance in multivariate analysis (controlled for age, LVEF and absolute cardiac risk).

Recent studies outlined the need to assess different aspects of depression in medically ill patients as well, such as demoralization. This concept has not been defined in current psychiatric nosography. In recent years, psychosomatic research has focused increasing attention on this issue. Psychosocial variables that were derived from psychosomatic research were translated into operational tools by a group of international researchers (Fava et al, 1995), such as Diagnostic Criteria for Psychosomatic Research (DCPR), whereby individual patients could be better diagnosed. Demoralization defined by the DCPR (Rafanelli et al, 2003) is a feeling state characterized by the patient's consciousness of having failed to meet his or her own expectations (or those of others) or being unable to cope with some pressing problems; the patient experiences feelings of helplessness, hopelessness or giving up. Using this definition, a recent study of ACS patients (Rafanelli et al, 2005) revealed that 20% of them were also demoralized. Among patients with major depression, 17% were not demoralized, and among demoralized patients, 7% did not meet the criteria for major depression. The treatment implications of the syndrome of demoralization as defined by the DCPR have not yet been established.

The negative impact of depression on post-ACS prognosis underscores the need for interventions to address these problems. Although antidepressants are effective in reducing depression in ACS patients (Frasure-Smith et al, 2006), their use in cardiac patients remains controversial. Moreover, the SADHART study (Glassman et al, 2002) tested the SSRI sertraline against placebo but found no significant differences in outcome over the 24 weeks of the trial. On the other hand, cognitive behavioral therapy (CBT) is a brief well-established and effective treatment for depression. Over 75% of patients show significant improvements. In earlier clinical trials, CBT has been found to

be as effective as imipramine in the treatment of depression. In addition, this approach has been found superior to other approaches and has been shown to be an effective treatment for depression for older adults and for those with severe depression. As relatively brief goal-oriented, collaborative, and emotionally supportive forms of treatment, cognitive-behavioral is generally well accepted by cardiac patients. Even though the only randomized behavioral intervention trial attempting to reduce morbidity and mortality in depressed patients with existing coronary disease (ENRICHD study) showed that changes in depression did not translate into improved survival, there remains the need to further investigate if treating depression can reduce the risk of morbidity and mortality in ACS patients.
In addition, an extensive body of evidence suggests the influence of psychological well-being in altering individual vulnerability to disease or quality of life. Ryff and Singer (1996) remark that, historically, mental health research is dramatically weighted on the side of psychological dysfunction and health is equated with the absence of illness rather than the presence of wellness. In a naive conceptualization, yet the one implicitly endorsed by the traditional psychiatric nosography, well-being and distress may be seen as mutually exclusive (i.e. well-being is lack of distress). According to this model, well-being should result from removal of distress. Yet, there is evidence both in psychiatric and psychosomatic research to call such views in question. Carol Ryff's multidimensional model of psychological well-being includes environmental mastery, personal growth, purpose in life, autonomy, self-acceptance and positive relations with others (Ryff, 1986). Ryff and Singer discussed the contours of positive human health, and how it is rooted in a biopsychosocial consideration of the patient. Since psychological well-being seemed to altering individual vulnerability to disease or quality of life, it has been found that therapy specifically addressed to the various aspects of well-being has yielded clinical benefits in improving quality of life in chronic and life-threatening illnesses. Well-being therapy, developed by GA Fava (1999), is a short-term, well-being-enhancing psychotherapeutic strategy based on Carol D. Ryff's model. It may be applied as an additional ingredient of cognitive behavioral packages. The first validation studies appeared to be promising (Fava et al, 2006).

Specific aims and preliminary findings

The specific aims of this project are to 1) assess, by reliable methods, the presence of DSM-IV mental depression (major and minor, chronic and acute) and DCPR demoralization in patients with a first episode of ACS; 2) evaluate the efficacy of CBT in combination with WBT and lifestyle modification versus standard CM in reducing psychological distress and improving well-being scores after treatment; 3) evaluate the efficacy of CBT in combination with WBT and lifestyle modification versus CM in reducing the risk of morbidity and mortality in depressed and/or demoralized patients after a first episode of acute myocardial infarction or unstable angina. A two-year follow-up of the patients' population will be performed.
The first validation studies on the application of sequential treatment of CBT with WBT and lifestyle modification in the residual phase of recurrent depression were carried on by the coordinator's group of research (Fava et al, 1998a, 1998b). The results appeared to be promising. The sequential approach has in fact yielded significant advantages in terms of relapse rates and number of episodes of depression, and has resulted in

enduring remission during a drug free state in the majority of patients during a six-year follow-up. Patients who received such treatment reported a substantially lower rate of relapse (40%) during the 6-year follow-up than the patients assigned to clinical management (90%). Such difference was significant, both in terms of comparison of mean survival time and survival analysis (Fava et al.,2004). The findings have dramatically outlined the importance of psychotherapy and clinical psychology in the prevention of relapse in recurrent depression. The sequential approach has been subsequently applied with success also in the U.K. (Paykel et al.,1999; Teasdale et al.,2000), Canada (Ma & Teasdale, 2002) and Netherlands (Bockting et al.,2005). A multicentre randomized controlled trial employing the PI's protocol is currently in progress in Germany. The findings of this sequential strategy have achieved further importance in view of the disappointing results of the U.S. mega-trial STAR*D, which has predominantly used sequenced pharmacological strategies (Rush et al., 2006).
We assume that the combination of CBT and WBT, including lifestyle modification, may yield more profound and enduring effects on psychological distress, cardiac morbidity and mortality than CBT alone.

Endpoints. As the primary end-point, the present research includes the improvement in depression as assessed by variations in overall CID score of at least 4.1 points, after CBT-WBT versus CM. The expected superiority of CBT-WBT versus CM is set to the 80%, at, if the pre/post treatment difference of CID scores is at least 4.1 points (Fava et al, 1998b). As secondary end-points the study includes: 1) the improvement of psychological distress and well-being evaluated through the variations in the overall Symptom Questionnaire (SQ) and Psychological Well-Being scales (PWB) scores; 2) the decrease of stress biomarker after CBT-WBT versus CM; 3) the reduction of cardiovascular major adverse events (cardiac mortality, recurrent heart attack and new hospitalization for cardiovascular causes) after CBT-WBT versus CM.

Study design and methods

The same protocol will be carried out in the two participating centres (Maggiore Hospital in Bologna and Molinette Hospital in Torino, Italy).
Participants will be patients recovering from a first episode of acute myocardial infarction or instable angina. Myocardial infarction will be documented by cardiac symptoms (presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without apparent non- cardiac source) and signs (acute congestive heart failure or cardiogenic shock in the absence of non-CHD causes) associated with ECG findings (characteristic evolutionary ST-T changes or new Q waves) and/or cardiac biomarkers (blood measures of myocardial necrosis, specifically CK, CK-MB, CK-MBm, or troponin, cTn). Instable angina will be documented by cardiac symptoms (chest pain lasting less than 20 minutes) with likely ECG findings (ST-segment depression and abnormal T-wave) in absence of myocardial necrosis biomarkers.
Medically eligible patients involved in the study have to meet, when screened 30 days after their index event, the following criteria: 1) a current diagnosis of at least one of the following: major or minor depression, dysthymia according to DSM-IV criteria, and demoralization according to DCPR criteria 2) no history of bipolar disorder (DSM-IV criteria), 3) no major depression with psychotic features, 4) no history of substance

abuse or dependency during the previous 12 months 5) no serious suicide risk 6) no current use of antidepressants 7) no current treatment with any form of psychotherapy 8) Mini-Mental State Examination score higher than 24; 9) written informed consent provided by the patient to participate. The patients' diagnoses will be established by the consensus of a psychiatrist and a clinical psychologist independently using the Structured Clinical Interview for DSM-IV (First et al, 1994). Patients who will meet all of the study's eligibility criteria will be administered, both at intake and at the end of the treatment, by the same clinical psychologist blind as to treatment assignment who had evaluated them on intake, both observer-rated (Paykel's Clinical Interview for Depression, CID, 1985) and self-rating questionnaires (Kellner's Symptom Questionnaire-SQ, 1987, and Ryff's Psychological Well-being Scales-PWB, 1989). Medically eligible patients with a prior episode of major depression will be enrolled if meeting the symptom criteria for a major or minor depressive episode for at least 7 rather than the usual 14 days. The DSM-IV duration criterion for dysthymia will not be changed.

After the initial assessment, patients will be randomized with a computer-generated program to 1 of 2 treatment groups: 1) cognitive behavioral treatment (CBT) combined with well-being therapy (WBT) according to a standardized protocol 2) standard clinical management (CM). In both groups treatment will consist of twelve, 45-minute sessions once a week and will be provided by 3 clinical psychologists, who will administer both types of interventions in the two groups. The usual format of CBT is one weekly therapy session coupled with daily practice exercises designed to help the patient apply CBT skills in their home environment. This approach involves several essential features: identifying and correcting inaccurate thoughts associated with depressed feelings (cognitive restructuring), helping patients to engage more often in enjoyable activities (behavioral activation), and enhancing problem-solving skills. The first of these components, cognitive restructuring, involves collaboration between the patient and the therapist to identify and modify habitual errors in thinking that are associated with depression. Depressed patients often experience distorted thoughts about themselves, their environment and their future. Information from the patient's current experience, past history, and future prospects is used to counter these distorted thoughts. In addition to self-critical thoughts, patients with depression typically cut back on activities that have the potential to be enjoyable to them, because they anticipate that such activities will not be worth their effort. Unfortunately, this usually results in a vicious cycle, where in depressed mood leads to less activity, which in turn results in further depressed mood, etc. The second component of CBT, behavioral activation, seeks to remedy this downward spiral by negotiating gradual increases in potentially rewarding activities with the patient. The aim of the therapy is also to make the patient aware of chronic and often subtle life stresses that exert harmful consequences on the individual over a certain amount of time. Examples may be unawareness of the longer time that an increasing age requires for recovering from demanding days, inadequate rest, prolonged anxiety, inappropriate sleeping habits, and inability to protect oneself from requests that exceed the potential of the individual. When patients are depressed, problems in daily living often seem insurmountable. In the final process, the CB therapist provides instruction and guidance in specific strategies for solving problems (e.g. breaking problems down into small steps). The techniques included in WBT that may be used in overcoming impairments in environmental mastery, purpose in life, personal growth, autonomy, self-acceptance and positive relations with others may

include: (a) cognitive restructuring (modification of automatic or irrational thoughts); (b) scheduling of activities (mastery, pleasure, and graded task assignments); (c) assertiveness training; (d) problem solving. CM will consist of reviewing the patients' clinical status, and providing the patient with support and advice if necessary. Specific interventions such as exposure strategies, diary work, and cognitive restructuring will not be allowed. The patient will be encouraged to share the main events that took place in the previous 2 weeks. Both CBT and CM intervention will be manualized. Treatment integrity will be checked by submitting 10 randomly selected sessions (5 involving CBT and 5 involving CM) to 2 independent assessors, who will have to rate the overall treatment integrity and identify all sessions. The treatment will be provided at Maggiore Hospital in Bologna, and at Molinette Hospital in Torino, in laboratory spaces expressly dedicated to the psychological interviews with the patients. The clinical psychologists involved in the study have to present substantial previous clinical experience with CBT and WBT, including treatment of depression also of patients with chronic disease or, more specifically, coronary disease.

The cardiologists involved in the study will evaluate the patients at intake and once every 6 months to monitor changes in clinical course of cardiac disease. Data from electrocardiogram, echocardiogram, X ray, blood pressure, blood samples (cholesterol levels, creatinine, glycosylated haemoglobin, C-reactive protein, coagulation/fibrynolysis biomarkers) and waist/hip ratio will be provided at intake. TIMI RISK SCORE for STEMI (Morrow et al, 2000) and GRACE RISK SCORE for UA/NSTEMI (Bassand et al, 2007) will also detected at intake for mortality risk within 1 month after patients' cardiac index episode.

Both before and after psychological treatment, among laboratory testing, the following biomarkers will be investigated: urinary cortisol excretion, blood DHEA-S level, blood glycosylated haemoglobin, coagulation/fibrinolysis markers, urinary norepinephrine, urinary epinephrine. The association of these biomarkers with stress increases health risk, regardless of the presence of psychiatric disorder (Lupien et al, 1998). Among blood laboratory testing, hyperhomocysteinemia levels will be also detected, since elevated homocysteine metabolism was established as an independent risk for vascular disease (the risk increase directly with total homocysteine level 6% to 7% for every 1 μmol/liter increase in total homocysteine level) (Folstein et al, 2007). Heart rate variability (HRV) will be also investigated. Decreased HRV, in fact, a predictor of mortality, is reduced in patients with major depressive disorder after ACS (Glassman et al, 2007). Moreover, markers of pathophysiological mechanisms implicated in ACS will be investigated since they provide incremental value over existing ischemic biomarkers. Systemic markers of inflammation such as elevated C-reactive protein (CRP) levels (Morrow et al, 1998) will be studied for its prognostic value (Biasucci et al, 1996).

Before and after psychological treatment, and then after 3, 6, 9, 12, 18 and 24 months the differences between the two groups in CID, SQ and PWB scores will be analyzed.

STATISTICAL PLAN

The sample size was calculated based on the results of previous studies carried out by the Coordinator of the present project. According to the statistical analyses performed in previous studies focusing on treatment efficacy (Fava et al, 1998), a sample size of 100 patients (50 per treatment group) seems appropriate. In the present study, to obtain the

same difference between the mean CID scores with a power of 80%, at least 16 subjects per arm are required according to calculations performed with the piface software (Lenth, 2001, 2006-2009). Multivariate ANOVA will be used to examine differences in dimensional psychological variables (i.e. CID total score, SQ and PWB scales scores) between patients assigned to CBT-WBT and CM at pre-intervention. Mixed-model ANOVA (Repeated Measures) will be performed to test differences between groups (CBT-WBT or CM) on the CID total score, the PWB scales, and the SQ scale scores at different follow-up evaluations. For the comparison between the means of the two groups (CBT-WBT vs CM) in the scores of psychological measures (CID, SQ e PWB) and in the values of the biomarkers, analysis of the covariance will be used, considering baseline scores as covariates. The missing data will be analyzed with the Intention-To-Treat procedure. Survival analysis will be used in order to evaluate the period of time occurred between baseline and new negative cardiac outcomes. The follow-up time considered for relapse will be 24 months after the end of the treatment. Survival analysis will be used for time until relapse into cardiac events. Among factors investigated as possible predictors of outcome, assignment to CBT in combination with WBT or to CM will be included. The Kaplan-Meier method will be used for estimating survival curves. When relapse is the event of interest, survival will be referred to relapse-free status. The log-rank test and Cox proportional hazards model will be included to compare any survival distributions for each of the factors considered. For all tests performed, the significance level will be set at 0.05, two-tailed.

Time schedule of the project

All the patients admitted to the Hospital starting from September 2009 for a first episode of myocardial infarction or unstable angina could be potentially involved in the study. The clinical picture will be evaluated by both means of ECG/echocardiogram charts and laboratory testing. At that time, cardiovascular risk factors, left ventricular ejection, HRV, TIMI and GRACE scores will be also provided. After one month of their admission, at their first control visit routinely scheduled by the cardiologists to check the clinical status of the patients, the clinical psychologists involved in the study will present to the patients the project to obtain informed consent. They will also administer interviews and questionnaires to select depressed patients. Among them, who were affected during the previous month by the presence of at least one of the following depressive emotional states such as DSM major or minor depression, dysthymia, DCPR demoralization, will be included in the study. The patients who will satisfy inclusion criteria will be randomized to one of the two treatments assignment. Both before and after the treatments, urinary and blood biomarkers of cardiac prognostic value will be detected. The duration of the study for each subject is expected to be 27-28 months. Included are 3-4 months of intervention and 24 months of follow-up. The duration of the overall study is expected to be 3 years for each patient. Every three months for the first year and then every 6 months for the following time, the patients will be reassessed through the same questionnaires by the same clinical psychologists who had evaluated them at the first assessment.

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