Is Depression the Wrong Treatment Target for Improving Outcome in Coronary Artery Disease?

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A significant relationship between depression and cardiac morbidity has been documented [1]. The identification of depression as an unfavorable marker of the clinical course in coronary artery disease (CAD) in the 1990s [2–4] generated the hope of improving the prognosis of cardiovascular disease with treatment of depression. This hope, however, has not survived the test of time. In a Cochrane review on randomized controlled clinical trials (RCTs) of any length of treatment and any length of follow-up [5], psychological and pharmacological interventions have shown a small yet clinically meaningful effect on depression outcomes in CAD patients. However, no beneficial effects on the reduction of mortality rates and cardiac events have been found. Indeed, in some cases, treatment of depression was found to entail negative physical consequences. There are several potential explanations, involving drugs and psychotherapy, which account for this phenomenon.

The Failure of Antidepressant Drugs

The evidence that is available in psychiatric settings suggests that the positive effects of antidepressant drugs are related to symptom severity [6]. Indeed, the Sertraline Antidepressant Heart Attack Randomized Trial (SAD-

HART) [7], on depressed patients after CAD, found that the effect of sertraline was greater in patients with severe and recurrent depression. It is also true that, in cardiac settings, mild depressive symptoms are sufficient to enhance cardiovascular risk even in the absence of major depressive disorder [8–11]. Antidepressant treatment could thus be successful in terms of cardiac prognosis only in the subgroup of cardiac patients with more severe depression, but not in those with milder depression at equally elevated cardiac risk.

It has been suggested that selective serotonin reuptake inhibitors (SSRIs) might ameliorate the adverse effect of depression on cardiovascular disease through the inhibition of platelet aggregation, even independently of changes in depression [12]. This potential benefit, however, is counteracted by recognized adverse cardiovascular side effects [13–15]. In particular, the use of SSRIs such as citalopram and escitalopram is associated with cases of arrhythmias and prolonged QTc interval on electrocardiogram in patients lacking cardiovascular disorders [16]. Licht et al. [17] found that all antidepressants, including SSRIs, have a lowering effect on cardiac vagal control that has been found to be associated with increased blood pressure and other metabolic abnormalities, such as unfavorable lipid profiles and high glucose levels [18].

It is also well recognized that the potential for drug-drug interactions increases with the number of medication used [19] and this is a common problem for cardiac patients. Labos et al. [20] found that the use of an SSRI combined with dual antiplatelet therapy (including clopidogrel and ASA) was associated with an increased risk of gastrointestinal bleeding, hemorrhagic stroke or other bleeding that either necessitated admission to hospital or occurred in hospital during follow-up, compared with ASA use alone. Again, such drug-drug interactions may counteract the potential benefits of SSRIs on platelet aggregation.

The modest effects of antidepressant drugs in improving depression and the lack of effects on cardiovascular prognosis may also depend on the loss of clinical effects refractory to dosage increase, with enhanced susceptibility to subsequent episodes of depression, observed after long-term use of antidepressant drugs [21]. In patients with bipolar illness, these phenomena may involve switching into mania/hypomania and/or episode acceleration [21] and account for the failure of antidepressant drugs to improve long-term cardiovascular outcome.

The Failure of Psychotherapy Trials

On the whole, standardized approaches for the treatment of depression by psychotherapy have also failed to provide benefit to cardiac patients in clinical trials. The ENRICH study [22] found significant improvements in patients' levels of depression and social support 6 months after initiation of cognitive-behavior therapy (CBT) compared with care as usual, even though differences between the arms diminished over time and were no longer present at 30 months. It is likely that the approach failed to affect cardiac prognosis due to the short-term nature of the effects.

In the same vein, the CREATE study [23] found no advantage in reducing depression with a dozen 50-min sessions of interpersonal psychotherapy (IPT) compared with weekly 20-min clinical management sessions with clinicians who encouraged adherence and gave information about depression, discussed medication use and provided reassurance [24]. The results of this trial suggested the possibility of the unfavorable effects of psychological treatment on both depression and the cardiocirculatory system. In fact, patients randomized to IPT reported fatigue more frequently than those assigned to clinical management. They also experienced a slight increase in systolic blood pressure at 12 weeks in comparison to a

slight decrease among patients receiving clinical management alone [23]. These negative effects could be partially explained by the reported paradoxically higher level of initial social adjustment as a predictor of a good response to IPT [25], even though the theoretical basis of IPT would suggest greater effectiveness in patients with lower levels of social functioning [26]. This critical issue should thus be examined in future research on the evaluation of the efficacy of IPT on both depression and survival in cardiac patients. Another important aspect to be considered in the light of the negative results of treatments for depression, such as IPT, is that cardiac depressed patients in 14% of cases do not adhere to their prescribed medication regimen [27]. This could explain the positive effects of sessions of clinical management based on encouraging adherence compared to IPT in the CREATE trial.

There is also the need to consider that certain treatments could be unsuitable for CAD patients. In fact, most of the depression interventions, used in the cited trials involving patients with CAD, were originally validated with outpatients with psychiatric problems seeking treatment. Therefore, acceptance by the broader population of patients with CAD cannot be assumed [22], as cardiac patients often do not agree with a diagnosis of depression nor do they seek treatment for depression [28]. The issue of satisfaction with treatment has been the focus of the Coronary Psychosocial Evaluation Studies (COPES) RCT [28]. An enhanced care intervention based on both the preference of the patients and the severity of depression was more accepted by CAD depressed subjects in comparison with usual care and significantly reduced depressive symptoms and major adverse cardiac events. Moreover, the authors of the cited study chose to include a 3-month observation period to identify patients with persistent depressive symptoms and thereby decreased the likelihood of a large reduction in depressive symptoms in the control group [28].

Is Depression the Right Target?

Another potential explanation for the failure of the treatment of depression to improve outcome in CAD is the fact that only some depressed cardiac patients may be at a high risk of morbidity and mortality. If there is a high-risk subtype of depression, it could be underrepresented in some studies and overrepresented in others [29], giving different results in RCTs. Certain clusters of symptoms could be more relevant for cardiac prognosis than others. For example, anhedonia and somatic symptoms, such as

sleeping difficulties and fatigue, were found to be more 'cardiotoxic' than cognitive symptoms [30–34]. Thus, the treatment of depression is unlikely to ameliorate cardiac prognosis without a significant reduction of such symptoms. These harmful symptoms could represent specific targets for interventions that may be different from interventions derived from general psychiatry [32]. On the other hand, cardiovascular risk could be the result of an association between typical symptoms of depression and other conditions, that were not considered so far as targets of treatment, such as vital exhaustion [35, 36], hopelessness [37–39], demoralization [40, 41], pessimism [42, 43] and rumination [44].

In the same vein, it is likely that psychotherapy protocols focusing on depressive symptoms in cardiac settings may overlook other important negative affective components associated with depression, such as anxiety, anger, hostility, distress or a general disposition toward negative affectivity and personality traits [43, 45–52]. These components that are associated with depression, if untreated, could interfere with medical outcomes due to a combination of the effects on inflammation, catecholamines, heart-rate variability and endothelial function, along with effects on health-promoting behaviors [53].

The most substantial benefits in relapse prevention of depression have been obtained with a sequential combination of treatment strategies encompassing a broad spectrum of therapeutic targets [54, 55]. CBT applied to patients who had remitted upon pharmacotherapy yielded significant advantages in the sequential approach, both in terms of relapse rate and/or residual symptomatology, compared with clinical management or treatment as usual. The focus of CBT should be both on deficits and enhancing strengths and potentialities, as evidence exists that certain dimensions of psychological well-being, such as a purpose in life, may play an important role in protecting against myocardial infarction [56]. Treatments specifically addressing the enhancement of positive functioning could give better results in terms of cardiac prognosis, even though this is yet to be tested.

Type A Behavior: A Reassessment Is Overdue

Ormel and de Jonge [57] suggested that the most plausible pathways mediating the effects of persistent/recurrent depression (apart from the type) on cardiac prognosis are behavioral, and act by making depressed CAD patients more susceptible to other CAD risk factors. It is thus not surprising that psychotherapeutic treatments

specifically geared to lifestyle modification have achieved impressive results in CAD [58–60]. A low-fat vegetarian diet, smoking cessation, stress management training and moderate exercise turned out to be effective secondary prevention strategies of CAD in several clinical trials [58, 61–67], leading to a significant decrease in coronary atherosclerosis, rehospitalizations and cardiovascular events.

One of the components addressed in some of the studies is type A behavior [68] – a set of psychological features such as free-floating hostility, time urgency and competitiveness – that was found to be significantly associated with an increased risk of cardiovascular disease [69]. Since the 1980s, hostility has emerged as the most important feature [70]. However, interpretation of many studies has been complicated by the use of self-rating instruments, which neither capture the motor-expressive features of type A behavior nor determine its prevalence. This psychological construct is thus often discarded as an obsolete formulation. There is evidence, however, for calling such views into question. On the basis of original descriptions and the most relevant studies on type A, in the Diagnostic Criteria for Psychosomatic Research (DCPR) [71–73] nine items were identified to diagnose type A behavior. According to the DCPR, patients with cardiac conditions who presented type A (up to one third of the population) tended to display minimization of psychological impact and possible life-threatening consequences of cardiac disease [74]. This finding is in line with previous studies documenting an overlap between type A behavior and both hypomania and hyperthymic temperament, which are subclinical manifestations of the bipolar spectrum [75–77]. Such association could explain both an increased cardiac risk in patients with bipolar disorders [78, 79] and a lack of improvement in cardiac prognosis after the treatment of depression. In CAD patients with type A behavior, depressive symptoms following a cardiovascular event may thus be part of a subsyndromal bipolar disorder.

More literature is appearing on the detrimental effects of the pharmacological treatment of depression in the course of bipolar disorder [21, 80]. When patients with type A behavior become depressed, improvement of mood may bring the patient back to the hypomanic condition. Thus, moving from physical inactivity to exhausting exercise or from anhedonia to excessive work involvement may have a detrimental effect on cardiac prognosis. The lack of benefits evident in heterogeneous samples may result from a balance between beneficial and harmful effects in different subgroups [81]. In depressed patients with a history of type A behavior, use of mood-elevating

strategies may be contraindicated. Psychotherapeutic strategies aimed at preventing reassumption of hypomanic features, particularly if they are concerned with illness behavior including underestimation of vulnerability to unhealthy habits and illness progression [82], may be more suitable. These patients should not be encouraged to return to their premorbid functioning, but rather to adopt a more adaptive lifestyle [83], e.g. developing the ability to recognize tiredness and take a rest. A Cochrane review by Whalley et al. [84] underlines that psychological treatments in cardiac patients are more effective in lowering depression if they include type A behavior among their therapeutic targets. Thus, the treatment of depression without addressing an inappropriate premorbid lifestyle may actually worsen the course of CAD in the subgroup of patients who display type A behavior.

Even though in the last decades type A behavior has attracted limited research interest, there is evidence suggesting that its modification through cognitive-behavioral strategies may lead to a significantly lower risk of cardiac recurrences [68, 85, 86].

It should be noted that many of the controversial results of research on type A behavior in cardiovascular disease may be due to an excessive reliance on questionnaires that miss the clinical and observational features which formed the basis of original observations [87]. The DCPR criteria for type A behavior incorporate such clinical information [71].

Future Prospects

Depression has attracted a considerable amount of research and funding in CAD. However, RCTs have failed to document a significant effect of its treatment on sub-

sequent prognosis of CAD, and the clinical implications of massive research are at present negligible. The role of depression and the use of antidepressant drugs have been supported by extensive pharmaceutical propaganda [88]. Indeed, the use of antidepressants in cardiology settings has risen dramatically since the early 1990s [89]. The basic message sold to the physicians was that a better cardiovascular outcome could be obtained by treating depression even in its milder forms with readily available medications. Depression was assimilated to 'bad cholesterol' and antidepressant drugs to statins, which none should be refused (well beyond the original indications). Type A behavior did not fit with this promotional picture and was thus censored by the special-interest groups that control medical information [88].

The time has come, however, to question the massive use of antidepressant drugs in cardiology settings and the current research priorities that do not acknowledge type A behavior, lifestyle and the longitudinal course of mood disorders [90]. Depression in CAD may simply be the final common pathway of a number of psychosomatic developments and may be a partial and misleading target for treatment. Both psychosocial assessment and intervention in cardiac patients should incorporate a wider range of clinical phenomena which may interact with depressive symptomatology and its treatment. Such phenomena include type A behavior, lifestyle, illness behavior and psychological well-being [90, 91].

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