Review Article

Treatment of Depression in Elderly Patients with Cardiovascular Disease: Research Data and Future Prospects

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In recent years, a number of psychosocial factors (stress, depression, social class, type A behaviour) have been added to the list of classical risk factors for cardiovascular disease (smoking, hypertension, cholesterol level, diabetes mellitus). In patients aged >65 years, depression remains the most common psychiatric disorder.[1,2] It has a negative relation with quality of life and has an additive effect on incapacity following physical illness.[3,4] It is a chronic disorder with a high recurrence index.[5] Depression in the elderly is under-diagnosed[1] and under-treated, since these patients as a group have some peculiarities: 1) they are usually excluded from research protocols; 2) the age factor alters the clinical symptoms of depression and thus the recommended therapy; and 3) the medical community tends to be uncertain about its correct treatment, especially when the patients exhibit more than one disease (a common occurrence at this age).

It appears, however, that depression is related with the prognosis (mortality and morbidity) of cardiovascular disease.[6-9] In one study,[10] the symptoms of depression in the elderly were considered to be an independent risk factor for coronary artery disease and mortality. Depression has also been independently associated with the risk of heart failure in older hypertensive patients.[11] This review will focus on investigating the occurrence of depression in patients aged >65 years with a view to determining a therapeutic approach. It will discuss the factors involved in the diagnosis of depression, the patient's clinical picture, the possible aetiology of the relation between cardiovascular disease and depression, and it will evaluate the recommended therapies with regard to both clinical entities.

Data collection

We carried out a search in the PubMed and PsychInfo databases for research publications from the period 1998-2008. The search criteria were: a) coronary heart disease, coronary artery disease, isch(a)emic heart disease, myocardial infarction, unstable angina, acute coronary syndrome, coronary bypass surgery, atherosclerosis, sudden death, ventricular fibrillation, or ventricular tachycardia; b) mortality, survival or prognosis, old age, older patients, elderly, Greek; and c) therapy depression, depressive symptoms, dysthymia, or mood.

Studies were excluded if: a) the diagnosis of depression was based solely on questionnaires; b) the diagnosis of depression was not clear according to the Diag-

nostic and Statistical Manual of Mental Disorders, DSM-IV;[12] c) the sample was ≤500 individuals in aetiological studies (Kuper et al criterion[13]); or d) only general symptoms of dysthymia and non-standardised questionnaires were studied.

A total of 18 studies satisfied the criteria (Table 1). Nine aetiological studies reported significant correlations between a depression measurement (mean depression score in questionnaire and/or indication in clinical interview) and a measure indicative of cardiovascular disease (sign of cardiovascular disease, hypertension) in patients of different sex. Nine prognostic studies found statistically significant correlations between a measure of depression and a measure indicative of cardiovascular disease (myocardial infarction, heart failure, sign of cardiovascular disease). None of the studies that fulfilled the criteria included a Greek population. In 4 aetiological and 4 prognostic studies the mortality rate was correlated with the diagnosis of depression.

Table 1. Studies of depression and cardiovascular disease in patients aged over 65 years.

Year	First author	Patients	Mortality
Aetiological studies:			
1998	Whooley[17] (a)	7518 women	+
2000	Ariyo[10] (a)	4493 CVD	+
2001	Penninx[3] (b)	2397 CVD	-
2003	Luukinen[22] (d)	915 CVD	+
2001	Abramson[11] (a)	4538 hypertensives	-
1998	Mendes de Leon[48] (a)	2391 women with CVD	-
1998	Penninx[68] (b)	3701 CVD	+
2002	Williams[23] (a)	2501 CVD	-
1998	Sesso[4] (a)	1305 men with CVD	-
Prognostic studies:			
1998	Koenig[14] (a)	542 HF	0
2000	Welin[61] (c)	275 first MI	+
2001	Penninx[3] (b)*	450 CVD	-
2003	Shiotani[69] (e)	1042 MI	-
2003	Carney[8] (a)	766 MI	+
2003	Brummett[66] (a)	1250 HF	+
1998	Krumholz[53] (a)	292 HF (before MI)	-
2001	Murberg[63] (f)	119 HF	-
2002	Romanelli[39] (a)	153 MI	+

*The study by Penninx et al[3] included both prognostic and aetiological measurements.
a: USA, b: Netherlands, c: Sweden, d: Finland, e: Japan, f: Norway. +: mortality rate reported; -: mortality rate not reported; 0 – zero mortality. CVD – cardiovascular disease; HF – heart failure; MI – myocardial infarction.

Diagnosis

One initial observation concerns the inhomogeneity of the measurements. There appeared to be no common choice of questionnaires (25 different questionnaires were used for the diagnosis of depression), nor any standard way of carrying out the statistical analysis or presenting the findings. One explanation given by the investigators[14-17] for the difficulty in diagnosing depression[12] in elderly patients was the alteration in symptoms with increasing age. For example, in patients aged >65 years there may be poor subjective memory or signs of senility that can be diagnosed as pure senility or Alzheimer's, without the patient's overall clinical picture being taken into account (Table 2). It is worth noting here that most researchers of this age group determined the diagnosis of depression secondarily, that is, after the occurrence of a cardiovascular event.[4,6,10,11,14,15,17,18,32,33]

The usual forms of depression that appear in the elderly are major depressive disorder[18] and the mild form (dysthymia) with depressive symptoms of mainly cognitive type.[6] Both forms have similar risk factors, but there are insufficient data regarding their treatment: e.g. paroxetine[19] seems to have a positive effect on major depressive disorder but not on the symptoms of depression. One particular form of depression that occurs in the elderly is reported in the literature as 'vascular depression'.[2] It is characterised by symptoms of apathy, psychomotor dysfunction, functional problems, and symptoms of senility but also reduced depressive fixation (such as guilt or low self esteem). Studies that used magnetic resonance imaging found changes in the brain's white matter and possible ischaemia. This particular form of depression seems to have a poor response to selective serotonin reuptake inhibitors.[20,21]

Clinical picture

The clinical picture[22,23] of the elderly person who comes to the cardiology clinic with symptoms of depression is usually as follows:

1. Reduced motivation for health behaviours: smoking, no physical exercise, not following indicated diet.

Table 2. Alterations in the symptoms of depression with increasing age.

- Reduced complaint of "sadness"
- Hypochondriasis and somatic concern with late onset (>60)
- Poor subjective memory or a dementia-like picture
- Start of neuroses at an advanced age (marked anxiety, obsessive-compulsive or hysterical symptoms)
- Apathy or poor motivation, conversion reactions

2. Feelings of social isolation.
3. Chronic anxiety concerning survival.
4. Low perception of emotional support from family and friends.
5. Dysfunctional defence mechanisms regarding health problems (e.g. refusal to accept actual state of health).
6. Failure to conform to doctor's instructions.
7. Anorexia (weight loss).
8. Loss of strength and energy.
9. May show symptoms of panic disorder or anxiety.

Summing up, the patient suffers from a low quality of life. It also appears that these patients are affected more by the prejudice of health care professionals, regarding the necessity of treatment at their age, than by the problems of co-morbidity of their diseases.[23] Depression is not a characteristic of old age and it is not supposed to be normal as people grow up. The majority of old people adjust successfully to different developmental stages. Symptoms such as social isolation, reduction of everyday activities (without apparent reason) and lack of initiative, anxiety and agitation are not considered consequences of old age but might be indications of depression. Unfortunately, most of the patients and their relatives do not acknowledge this fact and do not seek help.

Common pathophysiological mechanisms of depression and coronary artery disease

At this point, in order to gain a fuller understanding of the study of depression in the elderly, it should be noted that a possible explanation of the epidemiological correlation between depression and coronary artery disease is the pathophysiology of the disorder as it occurs in the general population. Although depression is traditionally considered as a psychiatric disorder, it is governed by pathophysiological mechanisms that are also related to cardiovascular function. Research has shown that the relation between depression and cardiovascular disease involves the following:

1. the function of the immune system[24] (Figure 1),
2. the hypothalamic-pituitary axis and the secretion of cytokines, interleukin (IL)-1 and IL-6[25,26] (Figure 1),

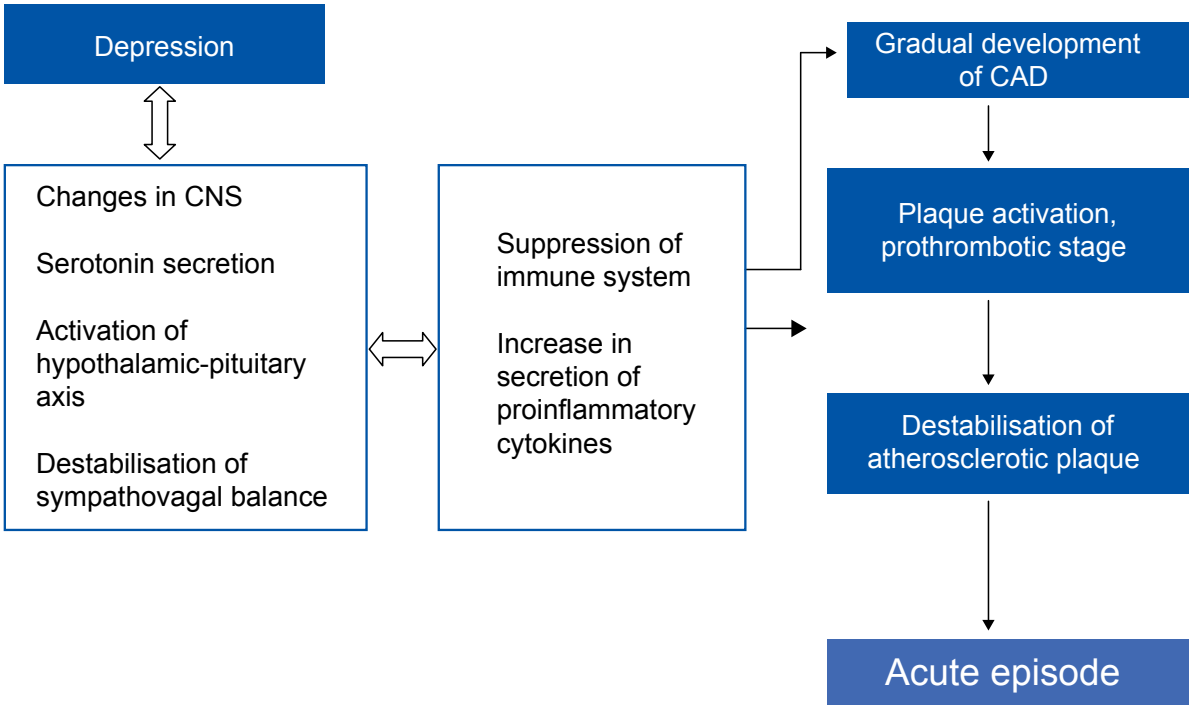

Figure 1. Depression can lead to changes in the central nervous system (CNS) that cause the secretion of neurohormones and activation of the hypothalamic-pituitary axis, resulting in destabilisation of the sympathovagal balance. Suppression of the immune system with the increase in secretion of proinflammatory cytokines can lead to the gradual development of coronary artery disease (CAD), plaque activation, and an acute episode.

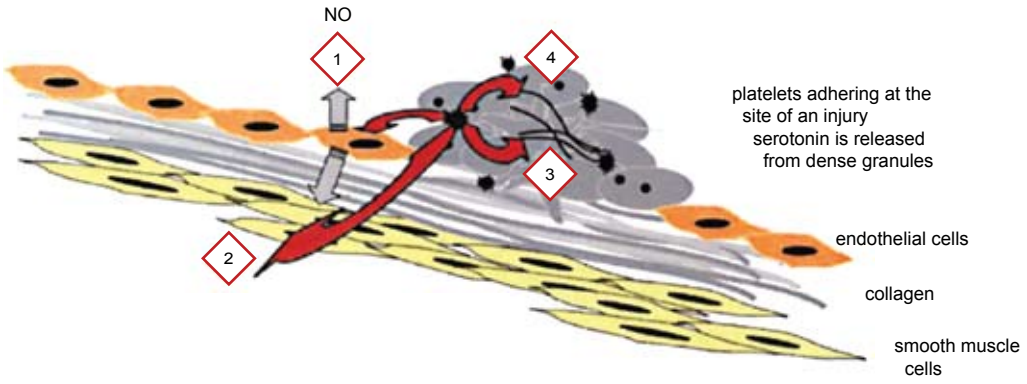

Figure 2. 1. Serotonin secretion in endothelial cells causes nitric oxide release. 2. Both substances cause vasodilation. 3,4. Activation of 5-HT2A receptors on the platelets, binding to A granules and thrombus stabilisation. 4. Interventions that affect serotonin can also affect haemostasis and thrombosis. (Reproduced with kind permission from Springer Science + Business Media: Cellular and molecular life sciences : CMLS, Serotonin reuptake inhibitors and cardiovascular diseases: a platelet connection, 62, 2005, 159-170, Maurer-Spurej E, Figure 1.)

3. arterial wall function[27] (Figure 2), and
4. the presence of the S allele of the serotonin transporter (5-HTTLPR)[19,28] (Figure 3),
5. the presence of 5-lipoxygenase (5-LOX).[29] Lipoxygenase is an anti-inflammatory enzyme responsible for the synthesis of arachidonic acid metabolites (leucotrienes). Increased activity by this enzyme is linked with the atherosclerotic process. In the brain, 5-LOX contributes to the regulation of neurotransmitters (e.g. glutamate) and affects the secretion of amyloid-beta. In animal studies, inhibition of 5-LOX seems to have an antidepressant effect.[29] For this reason, 5-LOX has been proposed as a common mechanism for atherosclerosis and depression.

Serotonin is considered to be the basic neurotransmitter that is associated with depression. A lack of serotonin in the synapses of brain cells is directly correlated with its clinical symptoms.[30] It also contributes to the manifestations of stress, including the clinical picture of depressive reactions as the result of physical diseases. Serotonin receptors, however, apart from the membrane of cells in the central nervous system, are also found in peripheral nervous system cells, endothelial cells and platelets.[30] As a result, serotonin also acts as a neurotransmitter for cardiac

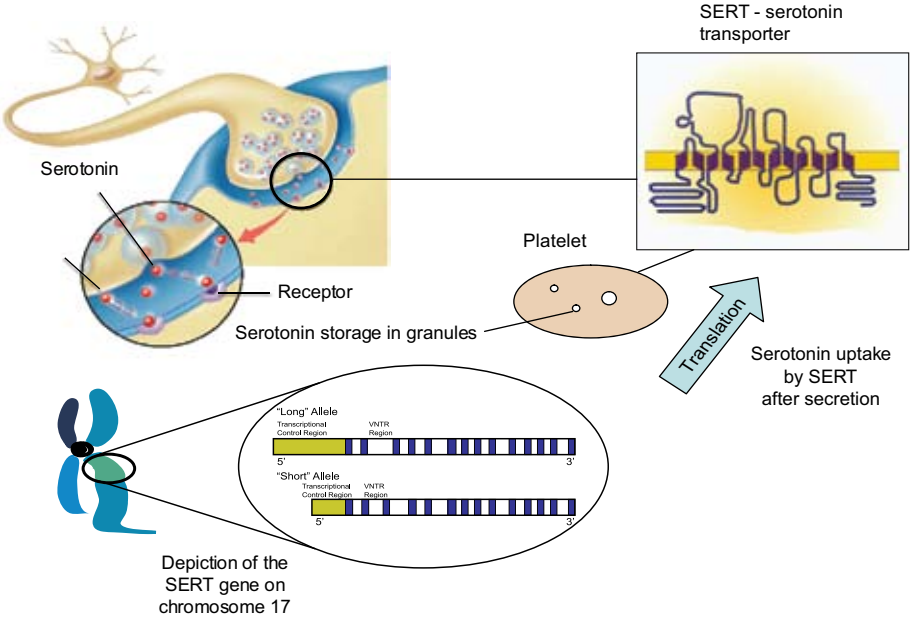

Figure 3. Translation of the SERT gene, serotonin uptake by SERT in the synapse, and its storage in platelet granules.

Table 3. Medications that can cause depression.

Cardiovascular drugs:
Beta-blockers
Methyldopa
Calcium channel blockers (e.g. nifedipine)
Digoxin
Corticosteroids:
Prednisolone
Analgesics:
Codeins
Opiates
COX-2 blockers (e.g. celecoxib, rofecoxib)
Anti-Parkinson:
Levo-dopa
Amantadine
Tetrabenazine
Psychotropic/antipsychotic:
Benzodiazepines

function, via the 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_7 receptors.[31] It regulates vascular tone, acts on cardiomyocytes and stimulates chemosensitive nerves in the heart.[31] Cardiac dysfunction is caused by a change in the blood concentration of serotonin.[32] The absence of peripheral serotonin synthesis (i.e. absence of serotonin mainly in platelets) is associated with heart failure. Elevated serotonin levels are associated with arrhythmias, possible heart block, and valvular fibrosis. In addition, serotonin appears to contribute to the development of the heart during the embryonic phase.[32]

When considering patients aged >65 years, it is worth noting that depression, like cardiovascular disease, is considered to be a progressive disorder. Especially in its endogenous form, it appears to start during puberty and to reoccur, with episodes of varying intensity each time, throughout adult life, a course that is similar to the progression of coronary artery disease. Thus, episodes of depression at a young age may cause early vascular damage and consequent atherosclerotic changes.[32] In the initial stages of atherosclerosis, the development of atherosclerotic plaque, by intensifying the activity of macrophages and lipid deposition, leads to the progression of coronary artery disease with increasing age.[31] At advanced stages, the latent inflammation reduces plaque stability and leads to an acute coronary syndrome.[24] This view is consistent with the picture of chronic depression in the elderly[32] in relation to cardiovascular function. It is why patients with chronic depression exhibit: a) an elevated index of platelet activation; b) endothelial dysfunction; c) a reduction in heart rate variability; and d) a reduction in baroreceptor sensitivity. It should be noted that only platelet function and heart rate variability improve under antidepressant therapy (selective serotonin reuptake inhibitors).[31]

In addition, taking drugs can cause depression: e.g. beta-blockers, methyldopa, calcium channel blockers, corticosteroids (prednisolone) (Table 3). It is important to note that 40% of those aged >65 years take an average of 5 drugs per week, while 12% take 10 drugs per week,[1] a fact that requires careful prescribing. Finally, diseases such as endocrine or metabolic disorders, chronic infections, organic encephalopathies, and some types of cancer can cause organic depression (Table 4).

Treatment

Depression in the elderly, as reported above, is characterised by chronic symptoms with frequently recurring episodes after each recovery. Its treatment model should follow that of any other chronic disease.[5] The basic goals of the treatment of depression are summarised in Table 5.

For the treatment of depression in elderly patients with cardiovascular disease, two methods are proposed: pharmacotherapy and psychotherapy. In elderly individuals with mild depression psychotherapy is equally as effective as medication.[33,34] In elderly patients with chronic depression the clinical picture is rather hard to evaluate: there are difficulties in modifying behaviour and way of life after an infarction, as

Table 4. Diseases that can cause organic depression.

Endocrine or metabolic disorders:
Hypo/hyperthyroidism
Cushing syndrome
Hypercalcaemia
Malignant anaemia
Folic acid deficiency
Chronic infections:
Syphilis
Brucellosis
Herpes zoster
Organic encephalopathies:
Cerebrovascular stroke
Central nervous system tumours
Parkinson's disease
Alzheimer's disease
Systemic lupus erythematosus
Cancer:
Pancreatic
Lung

Table 5. Goals and ways of treating depression in elderly patients with cardiovascular disease.

Goals	Achieved by
To reduce the likelihood of suicide or self-abandonment.	Frequent evaluation. Referral for psychiatric evaluation.
To treat the symptoms of depression in order for it not to progress to a chronic form.	Appropriate therapy (antidepressants, psychotherapy). Informing patients and relatives about depression.
To maximise the patient's functionality.	Treatment of concomitant physical diseases, management of adverse drug effects, referral to services for practical assistance.

well as difficulties in using drugs, with the result that the correlations found by research are unclear.

Pharmacotherapy

Elderly patients are often excluded from research protocols, with the result that our knowledge of drug effects in this group is deficient.[35-37] With the advance of age, the reduction in hepatic function causes a decrease in the capability for the metabolisation and deactivation of drugs. The reduction in renal function is accompanied by a reduction in the ability to eliminate drugs from the organism. There is an increase in drug half-lives, the patient becomes more prone to adverse drug effects, coexisting diseases may deteriorate, and it is easier for interactions to occur with other drugs that are being coadministered. Especially in the case of depression, the patient is at risk of dehydration and weight loss,[38,39] so that it is difficult to find the right dose. One conflict the clinician faces is the established guideline that the full clinical result of antidepressants is only usually apparent after 6-8 weeks of therapy (as opposed to 4 weeks in the young), which means a longer period of convalescence as well as a greater susceptibility to the adverse effects mentioned above. The safest method appears to be a conservative start and a gradual progression according to the result.[37]

The new-generation antidepressants promise safer results (Table 6). Selective serotonin reuptake inhibitors (SSRIs) and venlafaxine are preferred to other antidepressants because of their positive profile as regards side effects.[40]

More specifically, the action of SSRIs involves: a) an increase in serotonin in the receptors; b) a reduction in platelet activation; and c) a restoration of heart rate variability. These drugs show a low anticholinergic effect and almost zero arrhythmogenesis. Care is required if they are to be coadministered with antihypertensive medication, antilipidaemics, or regulators of heart rate that are metabolised by the isoenzymes CYP 2D6, CYP 3A4, CYP 1A and CYP 2C. Fluvoxamine is a powerful inhibitor of the latter two isoenzymes, while paroxetine and fluoxetine are powerful inhibitors of the first two (P450 enzymatic system), with the result that they inhibit both their own metabolisation and that of coadministered drugs, increasing the concentration of cardiological drugs in the plasma (Table 6).[41]

It must be stressed that the use of SSRIs should be based on a psychiatric evaluation, for which depression indexes (e.g. scales such as the Geriatric Depression Scale[42,43] or the Beck Depression Inventory[44,45]) are not a substitute, since these are affected by subjective factors at the time the patient is being evaluated and do not provide an overall picture. Malaise in the face of cardiac disease is a normal reaction, to which we should not automatically attribute a psychopathological dimension and consider it necessarily "treatable".

Another observation,[40] connected with the above, concerns the effect of SSRIs in patients who do not have depression. The effect of SSRIs on serotonin in the brain is well established; their effect on antithrombotic or pro-fibrinolytic agents may be demonstrated by biochemical studies of platelets. Platelets play an important role in cardiovascular disease, especially during the acute phase and the creation of thrombi. From animal studies we know that serotonin is essential for functional haemostasis. Thus, any drug that affects platelet serotonin also has an effect on cardiovascular disease. Nonetheless, SSRIs are not viewed as cardiovascular drugs. Studies that come out in support of the use of SSRIs have been mainly focused on the depression and not on the cardiovascular disease. The positive changes they cause in the course of the cardiovascular disease are considered

Table 6. Classification of adverse effects on cardiac function and drug interactions arising from antidepressant therapy (Leigh-Pemberton et al, 2006[18]).

Drug	Cardiovascular side effects	Interaction
Tricyclic amines (TCA):		
Amitriptyline	Increase in weight and QT interval, orthostatic hypotension, TdP	With medication that causes hypotension (e.g. CCBs, BBs)
Clomipramine	Increase in weight and QT interval, orthostatic hypotension, TdP	With medication that causes hypotension (e.g. CCBs, BBs)
Desipramine	Increase in weight and QT interval, orthostatic hypotension, TdP	With medication that causes hypotension (e.g. CCBs, BBs)
Imipramine	Increase in weight and QT interval, orthostatic hypotension, TdP	With medication that causes hypotension (e.g. CCBs, BBs)
Noritryptiline	Increase in weight and QT interval, orthostatic hypotension, TdP	
Selective serotonin reuptake inhibitors (SSRIs):		
Fluoxetine		Powerful CYPD6 inhibitor, mild inhibitor of 2C9, 3A4
Paroxetine		Powerful CYPD6 inhibitor
Sentraline		Mild CYPD6 inhibitor
Fluvoxamine		Powerful inhibitor of CY1A2, 2C19, mild inhibitor of 2C9, 3A4
Citalopram	Overdose causes QT prolongation	Low interaction (mild inhibitor of CY1A2, 2D6, 2C19)
Escitalopram		Low interaction (mild inhibitor of CYP)
Mixed action:		
Bupropion	Hypertension (in large doses), tachycardia	Low interaction
Duloxetin	Possible hypertension	Mild CYP2D6 inhibitor, very mild 1A2 inhibitor
Mirtazapine	Significant weight increase, mild orthostatic hypotension	Low interaction (mild inhibitor of CYP1A2, 2D6, 3A4)
Nefazodone	Mild orthostatic hypotension	Powerful CYP3A4 inhibitor, care needed when coadministered with CCBs and amiodarone, (mild CYP2D6 inhibitor)
Trazodone	Mild orthostatic hypotension, tachycardia	Care needed when coadministered with drugs causing hypotension (CCBs, BBs)
Venlafaxine	Hypertension (in large doses), tachycardia	Low interaction (mild CYP2D6 inhibitor)
Monoamine oxidase inhibitors (MAOIs):		
Phenelzine	Orthostatic hypotension, hypertensive crisis (especially if given with foods containing tyramine, trypophane or tyrosine)	Care needed when coadministered with drugs causing hypotension (CCBs, BBs)
Tranylcypromine	Orthostatic hypotension, hypertensive crisis (especially if given with foods containing tyramine, trypophane or tyrosine)	Care needed when coadministered with drugs causing hypotension (CCBs, BBs)
Isocarboxazid	Orthostatic hypotension, hypertensive crisis (especially if given with foods containing tyramine, trypophane or tyrosine)	Care needed when coadministered with drugs causing hypotension (CCBs, BBs)
Selegiline	Mild orthostatic hypotension	

BBs – beta blockers; CCBs – calcium channel blockers; TdP – *torsades de pointes.*

to be side effects of their antidepressant action.[46,47] So far, their use in a population without depression, but only cardiovascular disease, has not been investigated, while the mechanism through which they exert a positive effect on cardiovascular disease has not been studied adequately.[48]

Psychotherapy

Given the psychosocial characteristics (depression, stress, social isolation, recent loss, place of residence, low socio-economic level) that are related to cardiovascular diseases, a psychological approach is to be expected in any programme of intervention that aims either at prevention, or at case management during the acute phase, or at recovery after the clinical syndrome has become established. Historically, researchers[49,50] have tried so eagerly to establish a correlation between a psychological characteristic, type A personality, and the somatic disease, that they

have ignored for quite some time the psychological structures or behaviours that have a preventive effect on cardiovascular disease: i.e. the 'behaviour' of type A (anger, impulsiveness, hostility), and not the 'personality', seems to be related to the stimuli of the environment that the person translates as threatening, with the ultimate goal of sustaining personal control over the situation.

Recently, another type of personality has been related with cardiovascular disease: type D personality. It is characterised by negative thinking and a tendency for social isolation.[51] It should be stressed here that social and psychological support[52-54] become more strongly associated with good health as the age factor increases. Epidemiologically, there are further correlations between the mortality rate in all age groups and social isolation, recent loss, place of residence, and low socio-economic level[55-64] as risk factors.

Events that are perceived as stressful are those that cannot be controlled or are not foreseeable. In the definition of an event as stressful, the number and the awareness of necessary changes needed for the person's adjustment to the new situation play a significant role. The events defined as stressful share two characteristics: they cannot be controlled and they cannot be predicted. In studying the physiology of the individual who is experiencing such an event it appears that: a) there is a physiological specificity of reaction to the event;[65] b) there are latent reactions to stressful events, including bad health behaviours (smoking, alcohol consumption).[66] Without doubt, myocardial infarction (MI) is a stressful event. And, in this case, the environment of the person defines the stressful event as such, and also declares the appropriate ways to deal with it. The main areas of concern, also suggesting possible areas for treatment,[67-68] for older people suffering from both depression and CVD, are:

a) the maintenance of cognitive ability
b) the perception of the changes that may occur in life and habits
c) dealing with physical problems, such as insomnia, pain, anorexia (especially in patients where medical examinations are unclear as to the cause of the symptoms)
d) the family, and the patient's role within it
e) dealing with "negative" emotions, such as anger and aggression
f) end-stage issues.

Clinically, this is interpreted in terms of a specific range of psychological interventions. Of course, a significant part of the intervention concerns the reduction of one or more of the classical risk factors (e.g. smoking, bad diet), especially in the phases of prevention and of recovery. Specific forms of psychotherapy in the elderly have been reported: a) treating the generalised stress disturbance at the first appearance of the disease and the depression that preceded the cardiac episode; b) treating the stress and depression that accompany the disease at later stages, and mainly in the recovery phase.[70-73] In both cases, the proposed interventions appear to have better results in terms of physiological and psychological measurements of stress and depression, but do not affect mortality. The way feedback is provided by the medical team seems to play an important role in ensuring coordination in patient management.[71]

At this point, it is important to mention an attempt at combining cognitive behavioural therapy with SSRI medication, albeit not involving patients over 65 years old, in two basic clinical trials for the treatment of depression in patients with coronary artery disease: Enhancing Recovery in Coronary Heart Disease (ENRICHD),[62] and the Myocardial Infarction and Depression Intervention Trial (MIND-IT).[73] Both trials showed that patients who did not respond to antidepressant medication were at higher risk of an acute coronary syndrome. Both studies found satisfactory results in terms of depression, but mortality was unaffected. However, we have gleaned some important information concerning the choice of therapeutic approach:

a) The timing of the intervention is important. Limiting the intervention to the initial crisis (e.g. the first 6 months) is not sufficient, since the patient's condition is unstable and the depression is at its worst, or may even be an expected response to the crisis. This means that we draw research conclusions from a patient population who, after a few months, may not exhibit signs of depression. These patients may not be an appropriate sample in which to examine the hypothesis that by reducing depression we can reduce mortality and morbidity. On the other hand, from the moment when SSRI treatment is started we observe an immediate effect on cardiological indexes, whether there is improvement in the depression or not; it may thus be preferable to start treatment early.
b) The duration of the intervention is important. In ENRICHD the intervention lasted 6 months and after that time only medication was given for the prevention and treatment of new episodes of depression. It is possible that this interruption evened out the differences between those who

received cognitive behavioural therapy and those who did not. Long-term therapies might show better results in relation to depression and event-free survival.

c) The patient's cooperation is important. Admission to hospital for cardiovascular disease overshadows any emotional disturbance. That means that the patient's motivation to cooperate in treatment for depression is reduced. In research, and in the later creation of appropriate treatment programmes, we should take into account the suitability of our methods.

Conclusions

The different ways of evaluating depression (use of different questionnaires and/or clinical interview) cause methodological problems in its study. It is interesting, though, that despite the different measures, the indications for a powerful correlation between depression and cardiovascular disease are quite clear. More homogeneity in the measurements would lead to more correct results. It is also interesting that the number of review articles is almost the same as the number of research studies (we found 32 review articles). A possible explanation is that the heterogeneity in the samples, measurements, follow up, and statistical adjustments make the existing literature difficult to interpret, so that many investigators have tried to contribute. Another possible interpretation is that the results need "translating" into different specialties, and hence the training of various health care personnel should be considered essential.

Summing up, the treatment of depression in elderly patients with cardiovascular disease is considered feasible and mandatory, but it does not entail the reversal of the biological mechanisms that determine the relation between the two disorders. In some studies (Table 1) we also tend to relate depression with mortality rate. This may be the reason why we are unable to obtain clear results concerning the function of depression in cardiovascular disease. It is likely that mortality would be increased because of the co-existence of depression and organic disease. It is also likely that the low success rate in the treatment of depression in the elderly could cause that result. The only thing that seems clear in all this research activity is the necessity for the development and evaluation of more therapeutic protocols. Control of the disease –in the wider sense of mitigating the psychological malaise in the psychological dimension, and avoiding acute coronary episodes in the physical– could be a more acceptable parameter for the examination of the relation between the two disorders, as well as being more in touch with clinical practice.

The effect of depression on individual cardiovascular disorders (e.g. depression and hypertension, dyslipidaemia, atherosclerosis, arrhythmias, acute coronary syndrome, sudden death) has not been studied extensively (is it a prognostic risk factor, or is it the result of the disease, or treatment, or patient's life changes, and so a secondary risk factor?).[74,75]

The relation between other psychiatric disorders (e.g. stress disorder, panic disorder[76,77]) that could contribute to cardiovascular diseases has only recently been an object of study.[47]

Finally, a recent study[78] in the USA showed that patients' participation in a cardiac rehabilitation group reduced depression without the use of antidepressants. It seems that exercise, change in the way of life, and social support in such a group may offer a therapeutic route that combines treatment of both biological and psychological disease.

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