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Comorbidity of Depression with Physical Disorders: Research and Clinical Implications

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Depression is prevalent in patients with physical disorders, particularly in those with severe disorders such as cancer, stroke, and acute coronary syndrome. Depression has an adverse impact on the courses of these diseases that includes poor quality of life, more functional impairments, and a higher mortality rate. Patients with physical disorders are at higher risk of depression. This is particularly true for patients with genetic and epigenetic predictors, environmental vulnerabilities such as past depression, higher disability, and stressful life events. Such patients should be monitored closely. To appropriately manage depression in these patients, comprehensive and integrative care that includes antidepressant treatment (with considerations for adverse effects and drug interactions), treatment of the physical disorder, and collaborative care that consists of disease education, cognitive reframing, and modification of coping style should be provided. The objective of the present review was to present and summarize the prevalence, risk factors, clinical correlates, current pathophysiological aspects including genetics, and treatments for depression comorbid with physical disorders. In particular, we tried to focus on severe physical disorders with high mortality rates, such as cancer, stroke, and acute coronary syndrome, which are highly comorbid with depression. This review will enhance our current understanding of the association between depression and serious medical conditions, which will allow clinicians to develop more advanced and personalized treatment options for these patients in routine clinical practice.

Key Words: *Depression; Risk factors; Prognosis*

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INTRODUCTION

Depression refers to a state of low mood, loss of positive affect (markedly diminished interest and enjoyment in activities that were previously considered pleasurable), and a variety of emotional, cognitive, and behavioral symptoms including anhedonia, disrupted sleep and eating, worthlessness, and recurrent thought of death. Without treatment, depression is likely to be chronic, recurrent, and associated with increasing disability over time.[1] Depression has been predicted to be the leading cause of disease burden in 2030 by the World Health Organization (WHO).[2] Thus, the independent disability of depression might indicate an anticipated burden of depression in the context of physical disorders.

An emerging body of evidence demonstrates that depression and physical disorders are commonly comorbid.[3] This comorbidity is related to a poor quality of life (QoL), worse outcomes of the physical disorders, increased mortality, higher medical costs, greater disability, and a heightened functional impact than when depression or a medical disease is present alone.[4,5] On the basis of these findings, the comorbidity of depression and a physical disorder has been recognized as an increasingly important clinical and global health issue.[6] In this context, a burgeoning field of research is attempting to identify risk factors and effective treat-

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ments for depression in vulnerable patients with physical disorders, but this relationship remains under-recognized and untreated. Thus, this study aimed to review the prevalence, risk factors, and treatments for depression that manifests in patients with a physical disorder. In particular, this study focused on severe physical disorders with high mortality rates such as cancer, stroke, and acute coronary syndrome (ACS).

PREVALENCE OF DEPRESSION IN PHYSICAL DISORDERS

A strong body of evidence has suggested that depression is more frequent in patients with physical disorders and particularly among patients with multiple physical disorders. A 1-year prevalence study of 30,801 adults in the United States found that patients with chronic medical diseases were nearly three times as likely to get depressed (odds ratio [OR]: 2.6, confidence interval [CI]: 2.31-2.94) as were healthy controls.[7] Similarly, the 1-year prevalence study of depression among 245,400 patients from 60 countries conducted by the WHO[4] found that 9.3% to 18% of subjects with a single physical disorder had depression, whereas only 3.2% of subjects without a physical disorder had depression. Furthermore, nearly a quarter (23%) of patients with two or more physical conditions suffered from depression.

With respect to specific physical diseases, rates of depression vary according to methodological issues including the differential use of estimated time points and assessment scales. A systematic review of 31 prevalence studies using structured interviews revealed that 10.8% of cancer patients had major depressive disorder,[8] and a systematic review and meta-analysis of 61 studies that investigated depression after stroke found that 31% of all stroke survivors suffered from depression.[9] Additionally, another systematic review using a structured interview found that 19.8% of patients with ACS experienced major depression during their hospitalization.[10] The individual rate of depression prevalence in patients with physical disorders is about two- to three-fold higher than in the general population (6.6%);[11] similar results have been reported in Korea. Based on data from the National Health Insurance program, which is an obligatory national social insurance system that includes 99% of Korean citizens, the prevalence of depressive disorders in patients with breast cancer is 4.94%.[12] Additionally, according to the Korean National Health and Nutrition Examination Survey, 21.7% of patients with ACS and 25.5% of patients with stroke have experienced depression.[13]

Our research group has conducted several studies investigating the prevalence of depression in patients with various physical disorders including breast cancer (n=309), stroke (n=276), and ACS (n=969) who were treated at Chonnam National University. In these studies, major and minor depression were defined according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), and were assessed by using the Mini-International Neuropsychiatric Interview.[14] The prevalence rates of major and minor depressive disorder were 2.6% and 20.4%, respectively, in breast cancer patients;[15] 10.5% and 20.7%, respectively, in stroke patients;[16] and 18.3% and 20.7%, respectively, in ACS patients (Fig. 1).[17] In Korea, the prevalence rates of depression in patients with physical disorders are much higher than those in the general population (1-year prevalence of major depressive disorder: 1.7%; lifetime prevalence of major depressive disorder: 4.4%).[18]

IMPACT OF THE COMORBIDITY OF DEPRESSION ON THE PROGNOSIS OF PHYSICAL DISORDERS

The high prevalence of depression in patients with physical disorders suggests that this psychological disorder may significantly impact the medical outcomes of these individuals. With respect to health-related QoL, a previous study by Moussavi et al[4] reported that comorbid chronic depression incrementally worsens health state compared with depression alone, with any physical disorder alone, and with any combination of physical disorders without depression. In cancer patients, a poor QoL is more frequently associated with psychological conditions, including depression, than with sociodemographic or cancer-related variables.[19] Additionally, systematic reviews have revealed that the presence of post-stroke depression (PSD) has a role in determining the QoL of stroke patients[20] and that depression predicts subsequently poor QoL in ACS patients, even after control for confounding variables including baseline QoL and the severity of ACS.[21] Our research group also found that several psychological variables, including depression and awareness of disease status, are associated with QoL in terminal cancer patients in Korea.[22] Furthermore, PSD at baseline is associated with a poor

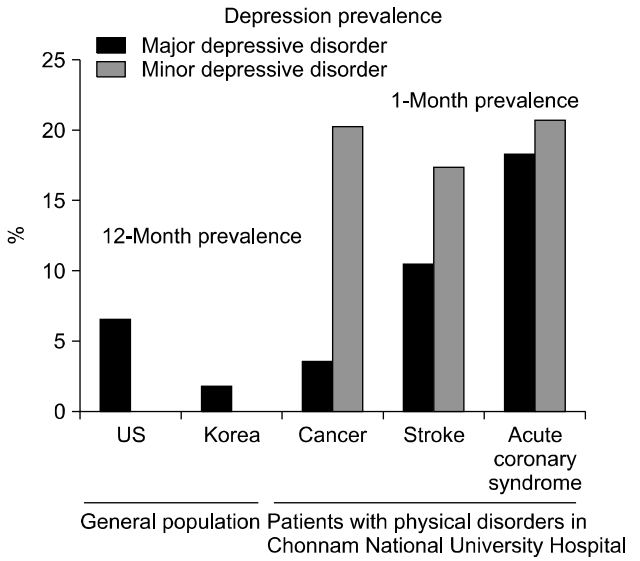

FIG. 1. Prevalence of depression among the general population and in patients with cancer, stroke, and acute coronary syndrome.

QoL both in the acute phase of stroke (2 weeks after the stroke) and in the subacute phase (3 months after stroke).[23-25] An analysis of longitudinal follow-up data from ACS patients, which included randomized trials of antidepressant treatments, revealed that depression was associated with a lower QoL, even in patients who had recently suffered from ACS, and that depression treatment was related to an improved QoL.[26] These findings underscore the importance of psychological assessment and intervention in patients with physical disorders, even during the acute stages of a disease.

With respect to functional impairments, recent studies have suggested that depressed patients with physical disorders exhibit significant deficits on both subjective and objective measures. A study of 30,801 adults found that patients with coexisting depression and physical disorders show greater functional impairments (OR: 2.48, 95% CI: 1.96-3.15), which suggests that comorbid depression independently influences functional disability.[7] A cardiological study showed that comorbid depression is prospectively associated with reduced ambulatory distance on a 6-min walk as well as self-documented functional disabilities.[27] Furthermore, the findings of randomized trials indicate that the treatment of depression effectively reduces both depressive symptoms and functional disabilities.[28] A recent review of 14 cohorts with a total of 4,498 stroke patients revealed that depression was negatively associated with functional outcomes,[29] and a study from our research group that assessed Korean stroke patients found that depression in the acute phase of stroke predicted poorer 1-year functional outcomes.[30,31]

With respect to disease progression and mortality, several large studies have investigated the association between mortality and depression in patients with physical disorders. A meta-analysis of 76 studies found that comorbid depression and cancer predicted increased mortality, even after adjustment for confounding medical factors (relative risk [RR]: 1.22, 95% CI: 1.14-1.30).[32] A recent systematic review suggested that mortality is an independent outcome of depression after stroke[33] and a subsequent study of 3,250 stroke patients observed that elevated mortality was associated with depression (hazard ratio [HR]: 1.27, 95% CI: 1.04-1.55).[34] Similarly, a recent systematic review of 53 studies investigating ACS, conducted by the American Heart Association, found that comorbid depression contributed to a 1.8- to 2.6-fold increment in all-cause mortality and a 2.3- to 2.9-fold increment in cardiac mortality.[35] Considering the stability of depression in patients with physical disorders for up to 10 years after stroke,[33] the detection and appropriate management of depression in these patients is evidently important and needed.

Finally, with respect to medical costs and the perception of medical symptoms, a systematic review of 31 studies demonstrated that a significantly higher number of medical symptoms were reported in patients with comorbid depression and chronic physical disorders such as diabetes, pulmonary disease, cardiac disease, and arthritis, even after adjustment for the severity of physical disorders.[3] Moreover, comorbid depression with physical disorders is associated with more frequent health care utilization and increased costs.[36] More specifically, patients with comorbid depression and ACS have a 15% to 53% increase in their 5-year cardiovascular costs[37] that cannot be explained by the increased utilization of mental health care but can be explained by increased visits to a family physician, medical specialists, and emergency costs.[38]

RISK FACTORS FOR DEPRESSION IN PATIENTS WITH PHYSICAL DISORDERS

In light of the high prevalence of depression and its enormous influence on patients with physical disorders, the identification of vulnerable individuals is an important step in the care of depression in these patients. To better understand the risk factors for depression in patients with physical disorders, a brief overview of the etiology of general depression is needed. It is well established that genetic factors act in concert with environmental factors across the lifespan to create a vulnerability to general depression.[39,40] Based on this etiological definition, the issues associated with the diagnosis and treatment of physical disorders such as cancer, stroke, and ACS likely act as environmental stressors. Therefore, a genetic vulnerability in combination with various environmental factors may predispose patients with physical disorders to develop depression. Many variables have been examined as predictors of depression in individual physical disorders. The present study aimed to review and evaluate predictors that were categorized as genetic vulnerabilities and predictors that were categorized as environmental factors, including sociodemographic and clinical variables.

1. Genetic vulnerability

The investigation of genetic associations in depression comorbid with physical disorders is a growing field of research. To date, however, few studies have evaluated the roles of candidate genes such as serotonin-related genes, genes that encode brain-derived neurotrophic factor (BDNF), and genes for cytokines. Genes coding for the serotonergic pathway have received increasing amounts of attention because serotonin (5-HT) is strongly associated with mood regulation. The 5-HT transporter (5-HTT), which eliminates 5-HT from the synaptic cleft and has a crucial role in determining serotonergic function, has a biallelic polymorphism in the 5-HTT gene-linked promoter region (5-HTTLPR). Among two polymorphisms including short (*s*) and long (*l*) alleles, the *s* allele decreases the expression of the 5-HTTLPR,[41] and it has been proposed that this allele generally increases the susceptibility to depression.[42] Similar to the 5-HTT gene, the 5-HT2a receptor (5-HTR2a) gene also regulates serotonergic signaling and two polymorphisms have been identified in the promoter region of this gene: an *Msp*I polymorphic site at position 102T/C and the 1438A/G polymorphism. The *C* allele for

the 102T/C polymorphism and the *AA* genotype for the 1438A/G polymorphism are related to lower 5-HTR2a expression[43,44] and to depression in general.[45] Another candidate, the BDNF gene, is crucial for neuronal survival and plasticity[46] and possesses several polymorphic markers including a single-nucleotide polymorphism (SNP) at nucleotide 196G/A that replaces valine (*val*) with methionine (*met*). The *met* allele is related to a decrease in the activity-dependent secretion of BDNF[47] and to depression.[48] Additionally, because cytokines are responsible for the regulation of inflammatory responses in patients with physical disorders and/or depression, genes that affect cytokine production are also good candidates for assessing genetic vulnerability to depression. Although the findings are inconsistent, some studies have suggested significant associations between depression and polymorphisms of cytokine genes such as TNF-α-308G/A, IL-1β-511C/T, and IL-10-1082G/A.[49]

Epigenetics, which refers to significantly long-lasting changes in genetic activity that are not due to alterations within a DNA sequence but to interactions between genes and environmental factors,[50] has recently emerged as a potential pathogenic factor underlying the development of depression.[51] Of the various epigenetic mechanisms, DNA methylation is the best studied because it is regarded as a highly stable epigenetic marker.[52] The increased methylation of gene promoters, including 5-HTTLPR and BDNF, is usually associated with lowered gene function and has been associated with depression in general.[53,54]

With respect to physical disorders in general, our research group found that patients with physical disorders are at a higher risk of depression occurrence if they possess the 5-HTTLPR *s* allele.[55] More recently, our group reported that the relationship between physical disorders and depression is strengthened in patients with a genetic susceptibility to exhibit a cytokine-mediated inflammatory response.[56]

Specifically in regards to cancer, the results from studies on the association between the 5-HTTLPR *s* allele and depression are inconsistent. The 5-HTTLPR *s* allele is associated with depression in head-and-neck cancer patients[57] but not in breast cancer patients.[58] Findings from our research group[59] support the latter study, which reported no associations of the 5-HTTLPR and 5-HTR2a genes with depressive disorder in Korean breast cancer patients. In terms of BDNF, data from a 1-year longitudinal study demonstrated that the *met*/*met* genotype was associated with depression 1 week after mastectomy and with persistent depression 1 year after mastectomy.[15] Regarding cytokines, the IL-1β-511 *T*/*T* genotype and increasing numbers of proinflammatory cytokine risk alleles are independently related to both baseline depression and persistent depression at the 1-year follow-up.[59,60] Furthermore, the methylation of the BDNF gene is related to a diagnosis of depression and severe depressive symptoms at both 1 week and 1 year after mastectomy for breast cancer.[61]

A recent meta-analysis of four studies, encompassing Korean data from a study conducted by the present authors, suggested that the 5-HTTLPR *s*/*s* genotype might be a risk factor for PSD.[62] Similarly, studies conducted in Korea and Hong Kong revealed that the 5-HTR2a 1438 *AA*[16] and 5-HTR2C[63] genotypes are associated with major PSD and PSD, respectively. The *met*/*met* BDNF genotype has been associated with PSD in both a community setting[64] and a hospital setting.[16] Not only the IL-4+33 *C*/*C* and IL-10-1082 *A*/*A* cytokine genotypes but also the increasing risk alleles of these two anti-inflammatory cytokine genotypes are associated with PSD.[65] Higher methylation of the 5-HTTLPR gene is associated with depression at 2 weeks and 1 year after stroke as well as with the exacerbation of depressive symptoms after 1 year.[66] Likewise, higher methylation of the BDNF gene is associated with baseline, persistent, and, in particular, incident depression as well as the exacerbation of depressive symptoms after 1 year.[67]

A literature review suggested that depressive symptoms in ACS patients are attributable, at least in part (nearly 20%), to common genetic vulnerabilities and variations related to inflammation.[68] This same review proposed that 5-HT is also a plausible candidate, although evidence is lacking regarding depression in ACS patients. The 5-HTTLPR *s* allele is associated with depression and subsequent cardiac events in both Caucasian[69] and East Asian[70] ACS patients. Likewise, both Caucasian[71] and East Asian[72] ACS patients with the BDNF *met*/*met* polymorphism are susceptible to depression. A 1-year longitudinal study of Korean ACS patients conducted by our research group found that the *s*/*s* genotype of the 5-HTTLPR was independently associated with the prevalence of depressive disorders and the persistence of these symptoms following ACS, but no significant associations were found with the 5-HTR2a polymorphisms.[17] Further analyses of genetic vulnerabilities to depression in ACS patients are ongoing with use of this cohort of Korean patients.

2. Environmental factors such as sociodemographic and clinical risk variables

A number of studies have evaluated various factors associated with depression in general and with individual physical disorders as predictors of depression in patients with physical disorders. These factors comprise sociodemographic factors such as age, gender, marital status, education, social support, and past histories of depression or physical disorders and clinical variables such as hypertension, diabetes, smoking, disability, and laboratory findings.[29,73]

In cancer patients, depressive symptoms are associated with sociodemographic factors including younger age, lower education, past depression history, absence of close relationships or social support, personality, hopelessness, and low self-esteem.[73] In contrast, clinical variables including cancer stage, tumor volume, type of surgery, chemotherapy, and radiotherapy have shown inconsistent results.[73,74] The data of 335 breast cancer patients admitted

to Hwasun Chonnam National University Hospital showed that past and family histories of depression were significantly associated with depression at baseline and that the number of metastatic axillary lymph nodes was associated with the persistence of depression at a follow-up assessment.[75] Additionally, the hopeful attitude of a patient was associated with depression via cellular immunity.[76]

The predictors of PSD have also been systematically investigated. A recent systematic review suggested that the consistent predictors of PSD included more severe neurological deficits and physical disabilities and pre-stroke depression, but no other associations were identified between depression and various sociodemographic factors.[29] A univariate analysis of data from 362 stroke patients admitted to Chonnam National University Hospital revealed that PSD was associated with older age, a higher number of stressful life events, poorer social support, severe disability, anterior stroke location, and previous histories of stroke and depression, whereas a multivariate analysis revealed that a higher number of life stresses and poorer social support were associated with PSD.[77]

It has been suggested that depression in ACS patients may be accounted for by demographic variables (less than 1%), disease indexes (7%), and psychological vulnerability (22%).[78] A study of predictors of depression in ACS patients reported that being female, previous depression, previous ACS, and smoking are consistently associated with depression.[79] The longitudinal data of 1,152 ACS patients admitted to Chonnam National University Hospital indicated that baseline depression was independently associated with being female, a lower educational level, previous ACS, and a higher heart rate. Moreover, incident depression (depression at 1 year after ACS without baseline depression) was predicted by current unemployment, family history of depression, higher baseline score on the Hamilton Depression Rating Scale (HAMD), and lower left ventricular ejection fraction, whereas persistent depression (depression at 1 year with baseline depression) was predicted by a higher baseline score on the HAMD and no depression treatment (unpublished data).

In summary, the early identification of patients with specific characteristics would facilitate the early implementation of useful management for these patients, which may prevent the development of depression. These populations include patients with a physical disorder who are at high risk of depression; cancer patients possessing vulnerable genes combined with previous and family histories of depression; stroke patients with pre-stroke depression, severe disability, greater levels of life stress, and poor support systems; and ACS patients who are female, had previous ACS, have a low educational level, and have higher heart rates. The risk factors for depression in patients with physical disorders are summarized in Table 1.

TABLE 1. Review of the risk factors of depression in patients with cancer, stroke, and acute coronary syndrome

	Genetic vulnerability	Environmental vulnerability
Cancer (especially breast cancer)	BDNF *met*/*met* genotype (baseline, persistence) IL-1β-511*T*/*T* genotype Increasing numbers of pro-inflammatory cytokine risk alleles BDNF hypermethylation (exon VI) (1week and 1 year after mastectomy)	History of depression (baseline) Family history of depression (baseline) Number of metastatic axillary lymph nodes (persistence)
Stroke	5-HTTLPR *s*/*s* genotype (baseline) 5-HTR2a 1438 *A*/*A* genotype (baseline) BDNF *met*/*met* genotype (baseline) IL-4 +33*C*/*C* genotype IL-10 -1082*A*/*A* genotype Increasing anti-inflammatory cytokine risk alleles 5-HTTLPR promoter hypermethylation (baseline, persistent, incident) BDNF hypermethylation (exon VI) (1week and 1year after stroke)	Pre-stroke depression Severe disability More stressful life stress Poor support system
Acute coronary syndrome	5-HTTLPR *s*/*s* genotype (baseline, persistence)	Female (baseline) Lower educational level (baseline) Previous acute coronary syndrome (baseline) Higher heart rate (baseline) Current unemployment (incidence) Family history of depression (incidence) Higher baseline HAMD score (incidence, persistence) Lower LVEF (incidence) No depression treatment (persistence)

BDNF: brain-derived neurotrophic factors, IL: interleukin, 5-HTTLPR: serotonin transporter gene linked promoter region, 5-HTR2a: serotonin 2a receptor, HAMD: Hamilton Depression Rating Scale, LVEF: left ventricular ejection fraction.

TREATMENT OF DEPRESSION IN PATIENTS WITH PHYSICAL DISORDERS

A majority of studies have suggested that depression in patients with physical disorders is common and will adversely influence the medical course of the physical disorder. As a result, many clinicians have questioned whether evidence-based psychotherapeutic and pharmacological interventions competent for depressed patients in general are as effective in patients with comorbid depression and physical disorders.

1. Psychological and pharmacological treatment

A recent meta-analysis including 44 randomized controlled trials aimed to determine the efficacy of antidepressants in patients with physical disorders.[80] These findings demonstrated that antidepressants were superior to a placebo (OR: 2.33, 95% CI: 1.80-3.00) for the treatment of depression, that their superiority was apparent within 4 to 5 weeks of the initiation of medication, and that this effect persisted after 18 weeks. In a study from our research group that assessed 732 depressive subjects, patients with comorbid physical disorders had a tendency to achieve less remission and less response across several different domains and took longer times to remission and response during the 12-week treatment period.[81] These data suggest that more careful evaluation and comprehensive management approaches are needed to promote treatment responses for depressive disorders in patients with a comorbid physical disorder.

A recent meta-analysis of six trials investigating cancer patients with depression[82] suggested that antidepressants are favored over placebo for managing depressive symptoms (RR: 1.56, 95% CI: 1.07-2.28) and that there were no significant differences between the dropout rates within the antidepressant and placebo groups (RR: 0.86, 95% CI: 0.47-1.56). Another recent meta-analysis of 21 trials evaluating patients in palliative care[83] found that antidepressant use was associated with significantly better responses than placebo at 4 to 5 weeks (OR: 1.93, 95% CI: 1.15-3.42), 6 to 8 weeks (OR: 2.25, 95% CI: 1.38-3.67), and 9 to 18 weeks (OR: 2.71, 95% CI: 1.50-4.91). Furthermore, the dropout rates were significantly greater at 9 to 18 weeks in the antidepressant group than in the placebo group. The increasing ORs for the superiority of antidepressants over extended periods of time indicate that antidepressant treatment for patients in palliative care should be maintained, despite the lack of early efficacy. Another recent meta-analysis of nine trials examined the relative efficacy of antidepressants for cancer-related depression and found that paroxetine, fluoxetine, and mianserin improved depression in cancer patients but the dropout rates were higher than with placebo.[84] A recent systematic review of five trials reported that psychotherapeutic treatments were reliably superior in reducing depressive symptoms,[85] although the conclusions were inconsistent for the overall effectiveness of psychosocial intervention with different scopes such as demographics, disease status, and treatment characteristics. Two review articles from our research group that describe this issue in Korean subjects are available.[86,87]

A meta-analysis of 16 trials that included 1,655 participants[88] found some evidence of the benefits of pharmacotherapy in PSD regarding remission and an improvement in depression scores. However, this study also observed an associated increment in side effects and no evidence of any benefits from psychological intervention. Therefore, antidepressant treatment for depression in stroke patients is tentatively supported, but this treatment modality must be considered in light of the associated increases in harmful effects. It is also recommended that antidepressants be prescribed with caution in patients with persistent depression after the occurrence of a stroke. Other than antidepressants, the use of statins might reduce the incidence of PSD.[89] Two review articles from our research group that describe this issue in Korean subjects are available.[90,91]

A meta-analysis of 16 randomized controlled trials[92] provided evidence of a small beneficial effect of psychological interventions relative to usual care for ACS patients (change in depression score OR: −0.81, 95% CI: −1.26-−0.36). However, no superiorities in treatment outcomes were observed among the varied psychological approaches. In terms of pharmacological interventions, there is some evidence that selective serotonin reuptake inhibitors (SSRIs) have a larger positive effect on depression outcomes than do placebo (depression remission; OR: 1.80, 95% CI: 1.18-2.74). Subsequent to that review, our research group carried out a randomized double-blind, placebo-controlled trial to estimate the efficacy of escitalopram for the treatment of depression in ACS patients[93] and found that escitalopram was preferable to placebo with respect to depression outcomes. Therefore, evidence as to the effectiveness of SSRIs for the treatment of depression in ACS patients may be strengthened by further studies in this population. An article on this issue from our research group is available.[94]

In conclusion, the use of antidepressants to manage depression in patients with physical disorders is supported by the literature, but clinicians should consider the associated adverse effects and drug interactions prior to prescribing this type of pharmacological intervention. The randomized controlled trials asessing treatments for depression in patients with physical disorders are summarized in Table 2.

2. Collaborative care

Collaborative care refers to a complex intervention that provides low levels of psychological support and medical consultation and adjusts the level of management on the basis of changes in symptom manifestation. This type of care is conducted by a nonmedical case manager in cooperation with the physician (generally the patient's family physician) and often involves the support and supervision of a mental health professional (typically a psychiatrist).[95] Collaborative care for patients with depression is clinically

TABLE 2. Review of randomized controlled trials assessing treatments for depression in patients with cancer, stroke, and acute coronary syndrome

	Proved efficacy in randomized controlled trials	Efficacy equal to placebo in randomized controlled trials
Cancer	Paroxetine	Desipramine
	Fluoxetine	Amitriptylline
	Mianserin	Imipramine
	Mirtazapine	
	Cognitive behavioral therapy	
	Supportive interventions	
	Problem solving therapy	
	Psychoeducation	
	Behavior therapy	
	Relaxation therapy	
	Mindfulness-based stress reduction	
	Psychosocial nurse counselling and intervention	
Stroke	Nortriptyline	Fluoxetine (2 trials)
	Amitriptyline	Sertraline
	Citalpram	Mianserin
	Fluoxetine (1 trial)	Methylphenidate
	Paroxetine	Motivational interviewing
	Reboxetine	Cognitive Behavioral therapy
	Trazodone (200 mg)	Psychoeducation
Acute coronary syndrome	Citalopram	Omega-3 add on treatment
	Escitalopram	Resource–Oriented Psychotherapy
	Fluoxetine	Interpersonal psychotherapy
	Sertraline (severe, prior episode)	
	Mirtazapine	
	Cognitive behavioral therapy	

effective[96] and, accordingly, the National Institute for Health and Care Excellence (NICE) recommends that patients with comorbid chronic medical illness and moderate-to-severe depression that is linked with functional impairments be treated with collaborative care.[97] Following the announcement of this recommendation, collaborative care has received increasing amounts of attention in terms of the effective management of depression in patients with physical disorders. Previous randomized controlled trials have demonstrated that collaborative care effectively reduces depressive symptoms, improves self-care in patients with a physical disorder, and improves QoL in ACS[98] and cancer[99] patients with depression. A recent meta-analysis of 14 trials found that nurse-delivered collaborative care was effective for the management of depression in patients with a variety of chronic physical disorders, including ACS, stroke, cancer, and diabetes.[100]

In summary, accumulating evidence describing the beneficial effect of collaborative care for the management of depression in patients with physical disorders provides important data about the treatment of depression. These findings have demonstrated that comprehensive and sustained treatment that is intensive, integrated with medical care, and systematically delivered by a well-trained and well-supervised team is needed to manage depression in patients with physical disorders.

CONCLUSIONS

Depression in patients with physical disorders is prevalent and adversely impacts the disease course of these patients with respect to QoL, functional impairments, and mortality. To effectively identify depression in patients with physical disorders at an early stage of the disease, patients with a higher risk of depression should be closely monitored and managed by use of comprehensive interventions that are composed of effective antidepressant treatments (with a consideration of their adverse effects and drug interactions in terms of treatment of physical disorders) in combination with supportive collaborative care.

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CONFLICT OF INTEREST STATEMENT

None declared.

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