Comorbidity of Depression with Physical Disorders: Research and Clinical Implications

Hee-Ju Kang¹, Seon-Young Kim², Kyung-Yeol Bae¹, Sung-Wan Kim¹, Il-Seon Shin¹, Jin-Sang Yoon¹ and Jae-Min Kim¹,*

¹Department of Psychiatry, Chonnam National University Medical School, Gwangju, ²Mental Health Clinic, Chonnam National University Hwasun Hospital, Hwasun, Korea

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

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 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.⁵ In this context, a burgeoning field of research is attempting to identify risk factors and effective treat-
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 WHO4 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 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 al4 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 patients20 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...
QoL both in the acute phase of stroke (2 weeks after the stroke) and in the subacute phase (3 months after stroke). 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. 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. A cardiovascular study showed that comorbid depression is prospectively associated with reduced ambulatory distance on a 6-min walk as well as self-reported functional disabilities. Furthermore, the findings of randomized trials indicate that the treatment of depression effectively reduces both depressive symptoms and functional disabilities. A recent review of 14 cohorts with a total of 4,498 stroke patients revealed that depression was negatively associated with functional outcomes, and a study from our research group that assessed Korean stroke patients found depression in the acute phase of stroke predicted poorer 1-year functional outcomes.

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). A recent systematic review suggested that mortality is an independent outcome of depression after stroke 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). 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 increase in all-cause mortality and a 2.3- to 2.9-fold increment in cardiac mortality. Considering the stability of depression in patients with physical disorders for up to 10 years after stroke, 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. Moreover, comorbid depression with physical disorders is associated with more frequent health care utilization and increased costs. More specifically, patients with co-morbid depression and ACS have a 15% to 53% increase in their 5-year cardiovascular costs 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.

**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. 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, and it has been proposed that this allele generally increases the susceptibility to depression. 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 MspI 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 1438AV/G polymorphism are related to lower 5-HTR2a expression and to depression in general. Another candidate, the BDNF gene, is crucial for neuronal survival and plasticity and possesses several polymorphic markers including a single-nucleotide polymorphism (SNP) at nucleotide 1966GA that replaces valine (val) with methionine (met). The met allele is related to a decrease in the activity-dependent secretion of BDNF and to depression. 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-511/C/T, and IL-10-1082G/A.

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, has recently emerged as a potential pathogenic factor underlying the development of depression. Of the various epigenetic mechanisms, DNA methylation is the best studied because it is regarded as a highly stable epigenetic marker. 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.

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. 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.

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 but not in breast cancer patients. Findings from our research group 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. 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. 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.

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. Similarly, studies conducted in Korea and Hong Kong revealed that the 5-HTR2a 1438 AA and 5-HTR2C genotypes are associated with major PSD and PSD, respectively. The met/met BDNF genotype has been associated with PSD in both a community setting and a hospital setting. 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. 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. 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.

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. 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 and East Asian ACS patients. Likewise, both Caucasian and East Asian 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. 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.

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. In contrast, clinical variables including cancer stage, tumor volume, type of surgery, chemotherapy, and radiotherapy have shown inconsistent results. The data of 335 breast cancer patients admitted...
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)** | History of depression (baseline) |
| BDNF met/met genotype (baseline, persistence) | Family history of depression (baseline) |
| IL-1β -511 T/T genotype | Number of metastatic axillary lymph nodes (persistence) |
| Increasing numbers of pro-inflammatory cytokine risk alleles | |
| BDNF hypermethylation (exon VI) (1 week and 1 year after mastectomy) | |
| **Stroke** | Pre-stroke depression |
| 5-HTTLPR s/s genotype (baseline) | Severe disability |
| 5-HTTLPR 5HTR2a 1438 A/A genotype (baseline) | More stressful life stress |
| BDNF met/met genotype (baseline) | Poor support system |
| IL-4 +33C/C genotype | |
| IL-10 -1082A/A genotype | |
| Increasing anti-inflammatory cytokine risk alleles | |
| 5-HTTLPR promoter hypermethylation (baseline, persistent, incident) | |
| BDNF hypermethylation (exon VI) (1 week and 1 year after stroke) | |
| **Acute coronary syndrome** | Female (baseline) |
| 5-HTTLPR s/s genotype (baseline, persistence) | 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. 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. 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 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 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. A recent systematic review of five trials reported that psychotherapeutic treatments were reliably superior in reducing depressive symptoms, 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.

A meta-analysis of 16 randomized controlled trials 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 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 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.

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 assessing 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). 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                                      | Amitriptyline                                            |
| 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                                               |
| Citalopram                                      | Mianserin                                                |
| Fluoxetine (1 trial)                            | Methylenidate                                            |
| 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\(^99\) 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.

ACKNOWLEDGEMENTS

This study was supported by grants of the Korea Health 21 R&D, Ministry of Health and Welfare, Republic of Korea (H112C0003).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Andrews G. Should depression be managed as a chronic disease? BMJ 2001;322:419-21.
2. World Health Organization. The global burden of disease: 2004 update. Geneva, Switzerland: WHO Press, 2008.
3. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 2007;29:147-55.
4. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 2007;370:851-8.
5. Naylor C, Parsonage M, McDaid D, Knapp M, Fossey M, Galea A. Long-term conditions and mental health. The cost of comorbidities. London: King’s Fund and Centre for Mental Health, 2012.
6. IOM (Institute of Medicine). Living well with chronic illness: a call for public health action. Washington, DC: The National Academies Press, 2012.
7. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry 2007;29:409-16.
8. Ng CG, Boks MP, Zainal NZ, de Wit NJ. The prevalence and pharmacotherapy of depression in cancer patients. J Affect Disord 2011;131:1-7.
9. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke 2014;9:1017-25.
10. Thomsbs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med 2006;21:30-9.
11. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617-27.
12. Kang JI, Sung NY, Park SJ, Lee CG, Lee BO. The epidemiology of psychiatric disorders among women with breast cancer in South Korea: analysis of national registry data. Psychooncology 2014;23:35-9.
13. So ES. Cardiovascular disease risk factors associated with depression among Korean adults with coronary artery disease and cerebrovascular disease. Asia Pac Psychiatry 2014. [Epub ahead of print]
14. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33.
15. Kim JM, Kim SW, Stewart R, Kim SY, Shin IS, Park MH, et al. Serotonergic and BDNF genes associated with depression 1 week and 1 year after mastectomy for breast cancer. Psychosom Med 2012;74:8-15.
16. Kim JM, Stewart R, Bae KY, Kim SW, Kang HJ, Shin IS, et al. Serotonergic and BDNF genes and risk of depression after stroke. J Affect Disord 2012;136:833-40.
17. Kim JM, Stewart R, Kang HJ, Bae KY, Kim SW, Shin IS, et al. Serotonergic genes and depressive disorder in acute coronary syndrome: The Korean depression in ACS (K-DEPACS) study. Eur Neuropsychopharmacol 2015. pii: S0924-977X(15)00039-5. [Epub ahead of print]
18. Cho MJ, Kim JK, Jeon HJ, Suh T, Chung IW, Hong JP, et al. Lifetime and 12-month prevalence of DSM-IV psychiatric disorders among Korean adults. J Nerv Ment Dis 2007;195:203-10.
19. Annunziata MA, Muzzatti B, Giovannianni L, Romito F, Cermio C, Mattioli V, et al. Is long-term cancer survivors’ quality of life comparable to that of the general population? An Italian study. Support Care Cancer. 2015. [Epub ahead of print]
20. Carod-Artal FJ, Egidio JA. Quality of life after stroke: the importance of a good recovery. Cerebrovasc Dis 2009;27 Suppl 1:204-14.
21. Dickens C, Cherrington A, McGowan L. Depression and health-related quality of life in people with coronary heart disease: a systematic review. Eur J Cardiovasc Nurs 2012;11:263-75.
22. Kim SY, Kim JM, Kim SW, Shin IS, Bae KY, Shin HJ, et al. Does awareness of terminal status influence survival and quality of life in terminally ill cancer patients? Psychooncology 2013. [Epub ahead of print]
23. Jeong BO, Kang HJ, Bae KY, Kim SW, Kim JM, Shin IS, et al. Determinants of quality of life in the acute stage following stroke. Psychiatry Invest 2012;9:127-33.
24. Kim SY, Kim JM, Stewart R, Kang HJ, Kim SW, Shin IS, et al. Influences of personality traits on quality of life after stroke. Eur Neurol 2013;69:185-92.
25. Yoon S, Jenog BO, Kang HJ, Kim SY, Bae KY, Kim SW, et al. Predictors of quality of life in subacute stage of stroke. J Kor Soc for Dep and Bip Disorders 2013;11:1-6.
26. Kim JM, Stewart R, Bae KY, Kang HJ, Kim SW, Shin IS, et al. Effects of depression co-morbidity and treatment on quality of life in patients with acute coronary syndrome: the Korean depression in ACS (K-DEPACS) and the escitalopram for depression in ACS (EsDEPACS) study. Psychol Med 2014;1:1-12.
27. Sullivan M, Levy WC, Russo JE, Spertus JA. Depression and health status in patients with advanced heart failure: a prospective study in tertiary care. J Card Fail 2004;10:390-6.
28. Von Korff M, Katon WJ, Lin EH, Ciechanowski P, Peterson D, Ludman EJ, et al. Functional outcomes of multi-condition collaborative care and successful ageing: results of randomised trial. BMJ 2011;343:d6612.
29. Kvitlubaev MA, Hackett ML. Part II: predictors of depression after stroke and impact of depression on stroke outcome: an updated systematic review of observational studies. Int J Stroke 2014;9:1026-36.
30. Kim JM, Stewart R, Park MS, Kang HJ, Kim SW, Shin IS, et al. Associations of BDNF genotype and promoter methylation with acute and long-term stroke outcomes in an East Asian cohort. PLoS One 2012;7:e51280.
31. Kang HJ, Stewart R, Park MS, Bae KY, Kim SW, Kim JM, et al. White matter hyperintensities and functional outcomes at 2 weeks and 1 year after stroke. Cerebrovasc Dis 2013;35:138-45.
32. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med 2010;40:1797-810.
33. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br J Psychiatry 2013;202:14-21.
34. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The long-term outcomes of depression up to 10 years after stroke; the South London Stroke Register. J Neurol Neurosurg Psychiatry
Depression in Physical Disorders

35. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al; American Heart Association Statistics Committee of the Council on Epidemiology and Prevention and the Council on Cardiovascular and Stroke Nursing. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation 2014;129:1350-69.

36. Bhattarai N, Charlton J, Rudisill C, Gulliford MC. Prevalence of depression and utilization of health care in single and multiple morbidity: a population-based cohort study. Psychol Med 2013;43:1423-31.

37. Rutledge T, Vaccarino V, Johnson BD, Bittner V, Olson MB, John BD, et al. Depression and cardiovascular health care costs among women with suspected myocardial ischemia: prospective results from the WISE (Women’s Ischemia Syndrome Evaluation) Study. J Am Coll Cardiol 2009;53:176-83.

38. Simon GE, VonKorff M, Barlow W. Health care costs of primary care patients with recognized depression. Arch Gen Psychiatry 1995;52:850-6.

39. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002;34:13-25.

40. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Kim YH, et al. Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. Biol Psychiatry 2007;62:423-9.

41. Heils A, Teufel A, Petri S, Seemann M, Bengel D, Balling U, et al. Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. J Neural Transm Gen Sect 1995;102:247-54.

42. Anguelova M, Benkelfat C, Turecki G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. Affective disorders. Mol Psychiatry 2003;8:574-91.

43. Polesskaya OO, Sokolov BP. Differential expression of the “C” and “T” alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. J Neurosci Res 2002;67:812-22.

44. Parsons MJ, D’Souza UM, Arranz MJ, Kerwin RW, Makoff AJ. The -1438A/G polymorphism in the 5-hydroxytryptamine type 2A receptor gene affects promoter activity. Biol Psychiatry 2004;56:406-10.

45. Enoch MA, Goldman D, Barnett R, Sher L, Mazzanti CM, Rosenthal NE. Association between seasonal affective disorder and the 5-HT2A promoter polymorphism, -1438G/A. Mol Psychiatry 1999;4:89-92.

46. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 2001;24:677-736.

47. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kalachana BS, Bertolino A, et al. The BDNF Val66Met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112:257-69.

48. Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med 2014;12:7.

49. Misener VL, Gomez L, Wigg KG, Luca P, King N, Kiss E, et al; International Consortium for Childhood-Onset Mood Disorders. Cytokine Genes TNF, IL1A, IL1B, IL6, IL1RN and IL10, and childhood-onset mood disorders. Neuropsychobiology 2008;58:71-80.

50. Bogdan R, Hyde LW, Hariri AR. A neurogenetics approach to understanding individual differences in brain, behavior, and risk for psychopathology. Mol Psychiatry 2013;18:288-99.

51. Uher R. Genes, environment, and individual differences in responding to treatment for depression. Harv Rev Psychiatry 2011;19:109-24.

52. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry 2009;65:760-9.

53. Fuchikami M, Morinobu S, Segawa M, Okamoto Y, Yamawaki S, Ozaki N, et al. DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression. PLoS One 2011;6:e23881.

54. Devlin AM, Brain U, Austin J, Oberlander TF. Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. PLoS One 2010;5:e12201.

55. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Modification by two genes of associations between general somatic health and incident depressive syndrome in older people. Psychosom Med 2009;71:286-91.

56. Kim JM, Stewart R, Kim SW, Kim SY, Bae KY, Kang HJ, et al. Physical health and incident late-life depression: modification by cytokine genes. Neurobiol Aging 2013;34:356.e1-9.

57. Gilbert J, Haman KL, Dietrich MS, Blakely RD, Shelton RC, Murphy BA. Depression in patients with head and neck cancer and a functional genetic polymorphism of the serotonin transporter gene. Head Neck 2012;34:359-64.

58. Grassi L, Rossi E, Cobianchi M, Aguirai L, Capozzo M, Martinis E, et al. Depression and serotonin transporter (5-HTTLPR) polymorphism in breast cancer patients. J Affect Disord 2010;124:346-50.

59. Kim JM, Kang HJ, Jang JE, Kim SY, Kim SW, Shin IS, et al. Interleukin-1 β -511C/T gene polymorphism and depression related to breast cancer. J of Kor Soc for Dep and Bip Disorders 2011;9:189-93.

60. Kim JM, Stewart R, Kim SY, Kang HJ, Jang JE, Kim SW, et al. A one year longitudinal study of cytokine genes and depression in breast cancer. J Affect Disord 2013;148:57-65.

61. Kang HJ, Kim JM, Kim SW, Shin IS, Kim HR, et al. A longitudinal study of BDNF promoter methylation and depression in breast cancer. Psychiatry Investig [in Press].

62. Mak KK, Kong WY, Mak A, Sharma VK, Ho RC. Polymorphisms of the serotonin transporter gene and post-stroke depression: a meta-analysis. J Neurol Neurosurg Psychiatry 2013;84:322-8.

63. Tang WK, Tang N, Liao CD, Liang HJ, Mok VC, Ungvari GS, et al. Serotonin receptor 2C gene polymorphism associated with post-stroke depression in Chinese patients. Genet Mol Res 2013;12:1546-53.

64. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Kim YH, et al. BDNF genotype potentially modifying the association between incident stroke and depression. Neurobiol Aging 2008;29:789-92.
65. Kim JM, Stewart R, Kim SW, Shin IS, Kim JT, Park MS, et al. Associations of cytokine gene polymorphisms with post-stroke depression. World J Biol Psychiatry 2012;13:579-87.
66. Kim JM, Stewart R, Kang HJ, Kim SW, Shin IS, Kim HR, et al. A longitudinal study of SLC6A4 DNA promoter methylation and poststroke depression. J Psychiatr Res 2013;47:1222-7.
67. Kim JM, Stewart R, Kang HJ, Kim SY, Kim SW, Shin IS, et al. A longitudinal study of BDNF promoter methylation and genotype with poststroke depression. J Affect Disord 2013;149:89-93.
68. McCaffery JM, Frasure-Smith N, Dubé MP, Théroux P, Rouleau GA, Duan Q, et al. Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation and serotonin. Psychosom Med 2006;68:187-200.
69. Nakatani D, Sato H, Shiotani I, Kinjo K, Mizuno H, et al; Osaka Acute Coronary Insufficiency Study Group. Influence of serotonin transporter gene polymorphism on depressive symptoms and new cardiac events after acute myocardial infarction. Am Heart J 2005;150:652-8.
70. Otte C, McCaffery J, Ali S, Whooley MA. Association of a serotonin transporter gene polymorphism on depressive symptoms and new cardiac events after acute myocardial infarction. Am J Cardiol 2005;100:1502-8.
71. Otte C, McCaffery J, Ali S, Whooley MA. Association of a serotonin transporter polymorphism (5-HTTLPR) with depression, perceived stress, and norepinephrine in patients with coronary disease: the Heart and Soul Study. Am J Psychiatry 2007;164:1379-84.
72. Liu YQ, Su GB, Duan CH, Wang JH, Liu HM, Feng N, et al. Brain-derived neurotrophic factor and serotonin transporter polymorphism (5-HTTLPR) with depression, perceived stress, and norepinephrine in patients with coronary disease: the Heart and Soul Study. Am J Psychiatry 2007;164:1379-84.
73. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005;330:702.
74. Bardwell WA, Natarajan L, Dimsdale JE, Rock CL, Mortimer JE, Hollenbach K, et al. Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol 2006;24:2420-7.
75. Kim SY, Stewart R, Kim SW, Yang SJ, Kim JM, Shin IS, et al. Predictors of depression in Korean breast cancer patients: A one year longitudinal study. Asia-Pacific Psychiatry 2012;4:250-7.
76. Kim SW, Kim SY, Kim JM, Park MH, Yoon JH, Shin MG, et al. Relationship between a hopeful attitude and cellular immunity in patients with breast cancer. Gen Hosp Psychiatry 2011;33:371-6.
77. Kang HJ, Bae KY, Kim SW, Kim JM, Shin IS, Kim JT, et al. Prevalence and risk factors of post-stroke depression. J of Kor Soc for Dep and Bip Disorders 2011;9:57-63.
78. Doyle F, McGee HM, Conroy RM, Delaney M. What predicts depressive symptoms post-acute coronary syndrome? J Clin Psychopharmacol 2014;34:72-9.
79. Naqvi TZ, Rafique AM, Andrews V, Rahban M, Mirocha J, Naqvi SS. Predictors of depressive symptoms post-acute coronary syndrome. Gen Mol Med 2007;4:339-51.
80. Rayner L, Price A, Evans A, Valsraj K, Hotopf M. Antidepressants for depression in physically ill people. Cochrane Database Syst Rev 2010;(3):CD007503.
81. Kim JM, Stewart R, Bae KY, Yang SJ, Yoon JH, Jung SW, et al. Physical comorbidity and 12-week treatment outcomes in Korean patients with depressive disorders: the CRESCEND study. J Psychosom Res 2011;71:311-8.
82. Laoutidis ZG, Mathiak K. Antidepressants in the treatment of depression/depressive symptoms in cancer patients: a systematic review and meta-analysis. BMC Psychiatry 2013;13:140.
83. Rayner L, Price A, Evans A, Valsraj K, Hotopf M, Higginson IJ. Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis. Palliat Med 2011;25:36-51.
84. Riblet N, Larson R, Watts BV, Holtzheimer P. Reevaluating the role of antidepressants in cancer-related depression: a systematic review and meta-analysis. Gen Hosp Psychiatry 2014;36:466-73.
85. Hart SL, Hoyt MA, Diefenbach M, Anderson DR, Kilbourn KM, Craft LL, et al. Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer. J Natl Cancer Inst 2012;104:990-1004.
86. Kim SW, Lee SY, Kim JM. Depression in cancer patients. Korean J Biol Psychiatry 2006;13:59-69.
87. Kim SY, Kim JM, Kim SW, Shin IS, Yoon JS, Shin HJ. Management of depression in terminally ill cancer patients. Korean J Psychopharmacol 2010;21:51-61.
88. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. Cochrane Database Syst Rev 2008;(4):CD003437.
89. Kim JM, Stewart R, Kang HJ, Bae KY, Kim SW, Shin IS, et al. A prospective study of statin use and poststroke depression. J Clin Psychopharmacol 2014;34:72-9.
90. Kim JM, Shin HY. Diagnosis and treatment of poststroke depression. Korean J Biol Psychiatry 2005;12:89-97.
91. Kang HJ, Kim SW, Kim JM, Shin IS, Yoon JS. Pathogenesis of post-stroke depression: a bio-psycho-social integrative model. J Korean Neuropsychiart Assoc 2011;50:347-53.
92. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. Cochrane Database Syst Rev 2011;(9):CD008012.
93. Kim JM, Bae KY, Stewart R, Jung BO, Kang HJ, Kim SW, et al. Escitalopram treatment for depressive disorder following acute coronary syndrome: a 24-week double-blind, placebo-controlled trial. J Clin Psychiatry 2015;76:62-8.
94. Kim JM, Bae KY, Kang HJ, Kim SW, Shin IS, Hong YJ, et al. Design and methodology for the Korean observational and escitalopram treatment studies of depression in acute coronary syndrome: K-DEPACS and EsDEPACS. Psychiatry Investig 2014;11:89-94.
95. Gunn J, Diggins J, Hegarty K, Blashki G. A systematic review of complex system interventions designed to increase recovery from depression in primary care. BMC Health Serv Res 2006;6:88.
96. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, et al. Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev 2012;10:CD006525.
97. NICE. Depression in adults with a chronic physical health
Depression in Physical Disorders

...problem. The NICE Guideline on Treatment and Management. National Clinical Practice Guideline 91. British Psychological Society and Royal College of Psychiatrists, 2010.

98. Coventry P, Lovell K, Dickens C, Bower P, Chew-Graham C, McElvenny D, et al. Integrated primary care for patients with mental and physical multimorbidity: cluster randomised controlled trial of collaborative care for patients with depression comorbid with diabetes or cardiovascular disease. BMJ 2015;350: h638.

99. Sharpe M, Walker J, Holm Hansen C, Martin P, Symeonides S, Gourley C, et al; SMaRT (Symptom Management Research Trials) Oncology-2 Team. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. Lancet 2014;384:1099-108.

100. Ekers D, Murphy R, Archer J, Ebenezer C, Kemp D, Gilbody S. Nurse-delivered collaborative care for depression and long-term physical conditions: a systematic review and meta-analysis. J Affect Disord 2013;149:14-22.