REVIEW ARTICLE

# Challenges in Treating Patients with Major Depressive Disorder: The Impact of Biological and Social Factors

Soichiro Sato · Tzung Lieh Yeh

**Abstract** Major depressive disorder (MDD) is frequently unrecognized and underdiagnosed by clinicians and thus remains untreated or inappropriately treated in routine clinical practice. Although the symptoms of MDD are widely acknowledged and recognized by clinicians, numerous epidemiological studies have reported that this disorder is more prevalent than had previously been thought, and that it is challenging to diagnose and treat, particularly because somatic symptoms and comorbid conditions are common in real clinical situations. MDD is associated with increased morbidity and mortality as well as with higher healthcare costs and more severe functional impairment. Therefore, optimal treatment for MDD should include collaboration focussed on comorbid physical diseases, rehabilitation aimed at restoring social functioning, and pharmacotherapy designed to ensure complete remission including psychological and physical symptoms, as well as functional recovery.

S. Sato (✉)
Zikei Hospital/Zikei Institute of Psychiatry, 100-2
Urayasuhonmachi, Southern Ward, Okayama City,
Okayama, Japan
e-mail: soichiro@ja2.so-net.ne.jp

T. L. Yeh
Department of Psychiatry, National Cheng Kung University
Hospital, College of Medicine, National Cheng Kung University,
Tainan, Taiwan

## 1 Introduction

Major depressive disorder (MDD) is so common a mental illness that almost all physicians, irrespective of specialty and location, will see patients with this condition. Indeed, unipolar major depression is currently the fourth leading contributor to the global disease burden. According to the Global Burden of Disease Study, unipolar major depression will be ranked as the second leading cause of disability-adjusted life-years, after ischaemic heart disease, in 2020. In 2030, it is likely to be the leading cause of disability-adjusted life-years [1, 2].

According to the nationwide survey conducted during 2001–2003, the lifetime prevalence of MDD is 16.6 %, and its 12-month prevalence is 6.7 % in the USA [3]. In addition, a worldwide survey conducted during 2001–2003 by the World Health Organization found that the 12-month prevalence of mood disorders in the USA is 9.6 % and 4.2 % in Europe but only 2.6 % in Korea, 3.1 % in Japan, 2.5 % in Beijing and 1.7 % in Shanghai [4].

According to a survey conducted by the Ministry of Health, Welfare and Labour in Japan, the number of patients with mood disorders, including MDD and bipolar disorder, has increased from 433,000 in 1996 to 1,041,000 in 2008 [5]. This phenomenon reflects several changes in Japanese psychiatric care, including the shift from traditional observation-based diagnosis to the use of international classifications, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases and Related Health Problems (ICD). The increasing familiarity of Japanese individuals with the term 'depression' has led to less hesitance among some people, especially those who are younger, in visiting a mental health clinic to address stress at work or school. Although the statistics may include some patients with

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mood disorders other than MDD, the number of patients diagnosed with MDD in clinical settings has certainly been increasing.

The prevalence of MDD in east Asian countries has long been underestimated. On the other hand, the suicide rate in east Asian countries, such as South Korea and Japan, has been higher than that in other countries [4]. These phenomena may be related to the cultural characteristics of this region. However, east Asian values have changed, and MDD must be treated appropriately to enable patients to live fulfilling lives. MDD treatment should not be limited to efforts to improve patients' symptoms but should also focus on patients' dignity and contribution to society.

According to some research, 30–50 % of MDD patients have severe depression, and more than 60 % show severe role impairment [3, 6, 7]. In addition, sequenced treatment alternatives to relieve depression (STAR*D) trials demonstrated that approximately 30 % of patients with MDD do not achieve remission after four antidepressant treatments but continue to experience significant impairment [8]. Therefore, approximately 30 % of MDD patients seem to have treatment-resistant depression.

Risk factors for treatment-resistant depression include comorbid psychiatric and physical conditions, younger age at onset, severe depression at baseline, inadequate dose and duration of treatment, socioeconomic issues and suicidal ideation [8]. Therefore, both biological and social factors are involved in treatment-resistant depression.

## 2 Biological Factors

### 2.1 Physical Symptoms in Major Depressive Disorder

Although MDD is classified as a mood disorder, physical symptoms are common in patients with the DSM-IV [9] diagnosis of MDD. DSM-IV specifies nine criteria, including five psychological and four physical symptoms, for MDD. Insomnia, appetite and weight change, psychomotor retardation/agitation and lethargy/fatigue constitute the physical symptoms, and these can be very important indicators of depression. Physical symptoms may be either the cause or the consequence of depression.

According to Nakao et al. [10], the majority of depressed patients complain about some kind of physical symptoms, such as fatigue, nausea, pain, and so on. The rates of fatigue, insomnia and nausea among patients with depression have been reported to be 86 %, 79 %, and 51 %, respectively (Table 1) [10]. The importance of physical symptoms in MDD was also replicated in a recent study that was conducted China, in which physical symptoms were highly associated with MDD and anxiety, regardless of the presence of underlying medical diseases [11].

Indeed, physical symptoms are very common among patients with MDD.

It was also reported that patients with MDD experience physical symptoms such as fatigue and loss of energy [12]. Indeed, approximately 90 % of patients reported physical symptoms [13]. Physical symptoms are not related to the severity of MDD. In general, changes in physical symptoms are the first changes of which patients with MDD are aware. These somatic symptoms are so varied that patients may consult primary physicians rather than psychiatrists for help. However, physical examinations may show few remarkable results, suggesting that the symptoms may be related to MDD. This indirect route of help-seeking may delay both referral to psychiatric clinics and the diagnosis and treatment of MDD; these delays can cause poor treatment outcomes. Indeed, it has reported that approximately 30 % of patients with MDD experience physical symptoms for more than 5 years before receiving the proper diagnosis [14–16].

Most depressed patients who fail to achieve remission have residual physical and psychological symptoms and the outcomes of patients with and without residual symptoms differ [16]. One study found that patients with residual symptoms had a three times higher risk of relapse compared with patients without residual symptoms [17]. More than 10 % of patients who complain about one to three physical symptoms are likely to have a mood disorder. In addition, as the number of nonspecific physical symptoms increases, the likelihood of having a mood disorder also increases [13].

Table 1 Proportion of somatic symptoms in patients with depression

| Symptoms | Depressed patients reporting symptom (%) |
|---|---|
| Fatigue | 86 |
| Insomnia | 79 |
| Nausea | 51 |
| Dyspnoea | 38 |
| Palpitations | 38 |
| Back pain | 36 |
| Diarrhoea | 29 |
| Headache | 28 |
| Chest pain | 27 |
| Sexual dysfunction | 23 |
| Pain in extremities | 20 |
| Dizziness | 19 |
| Abdominal pain | 18 |
| Tinnitus | 18 |
| Joint or limb pain | 16 |

Adapted from Nakao et al. [10]

Physical symptoms may also influence treatment response. In particular somatic symptoms do not adequately respond to selective serotonin reuptake inhibitors (SSRIs). However, serotonin and norepinephrine reuptake inhibitors (SNRIs) may have differential efficacy in MDD with physical symptoms compared to SSRIs because they inhibit both serotonin and norepinephrine, which are major neurotransmitters in pain pathways. In fact, SNRIs are approved for the treatment of pain-related diseases other than MDD itself [18, 19]. Therefore, we may need clinical trial data with SNRIs for the control of physical symptoms because SNRIs may cause further improvement from partial response with SSRIs in MDD patients with physical symptoms [20]. A recent naturalistic, randomized trial found that treatment with SSRIs was associated with different effects as a function of the presence of physical symptoms; emotional symptoms were three times more likely to respond to this treatment than were physical symptoms [21]. After 9 months of SSRI treatment, emotional symptoms improved first, and feelings of positive wellbeing followed. Physical symptoms improved later, with non painful somatic symptoms improving third and painful somatic symptoms improving last. Therefore, the study indicates a possible relationship of physical symptoms and treatment outcomes, which should be more intensively studied in adequately powered and well-controlled clinical trials [21].

## 2.2 Comorbid Physical Diseases

MDD is considered an important risk factor for physical diseases. According to the STAR*D study of 1,500 patients, the total prevalence of physical diseases was 53 %. Patients who were older, had lower incomes, were unemployed, were less educated and had had depression for a longer duration were at higher risk of developing various medical disease. Musculoskeletal diseases, found in 43 % of patients with MDD, were especially prevalent (Table 2) [22].

**Table 2** Prevalence of comorbid physical diseases in patients with depression

| Disease/system | Prevalence (%) |
| --- | --- |
| Eyes, ears, nose, throat and larynx | 45 |
| Musculoskeletal | 43 |
| Respiratory | 32 |
| Neurological | 27 |
| Upper gastrointestinal | 26 |
| Genitourinary | 25 |
| Endocrine | 24 |

Adapted from Perahia et al. [20]

## 2.3 Myocardial Infarction

According to a naturalistic study including 896 post-myocardial infarction (MI) patients, the level of depression symptoms during admission for MI was found to be more closely associated with long-term survival than the level at 1 year, particularly in patients with moderate to severe levels of MDD, indicating that that the presumed cardiovascular mechanisms linking MDD to cardiac mortality may be more or less permanent for them [23]. Depression is a strong independent risk factor for ischaemic heart disease, and it alters platelet physiology in a way that may increase the risk of thrombus formation. Depression has a negative prognostic effect on mortality after acute MI. Follow-up of patients with MI more than 6 years after discharge indicated that the severity of depression was predictive of mortality and was positively associated with mortality [23].

## 2.4 Diabetes Mellitus

A meta-analysis of 42 studies showed that the risk of comorbid MDD in patients with diabetes was twice as high as that for people without diabetes [24]. MDD that is comorbid with diabetes tends to be more severe, chronic and prone to recurrence. Moreover, those with diabetes and comorbid depression are less likely to follow treatment recommendations (e.g. dietary restrictions, medication regimens, and blood glucose monitoring), which leads to poor outcomes. Depression is associated with a 60 % increased risk of type 2 diabetes [24].

## 2.5 Chronic Physical Diseases plus Major Depressive Disorder

Patients with chronic physical diseases often have MDD. Indeed, the prevalence of MDD is higher in medically ill patients [25]. Comorbid MDD exacerbates patients' physical symptoms and decreases their pain threshold, which increases functional impairment. As a result, treatment adherence is reduced. Depression is also associated with adverse health behaviours and increased morbidity and mortality.

The presence of comorbid physical diseases is among the important risk factors for poor outcomes in MDD, and MDD is highly prevalent in patients with various medical conditions. Twenty-five per cent of patients with cancer, one-third of patients with Alzheimer's disease, and half of patients with Parkinson's disease have major depression, rendering MDD a potential cause of poor prognosis in such conditions [26, 27].

According to a global survey of 60 countries [28], the 12-month prevalence of MDD, angina and asthma was

3.2 %, 4.5 % and 3.3 %, respectively, in the absence of comorbid conditions. However, the average prevalence of comorbid depression in patients with one or more chronic physical disorders was between 9.3 % and 23.0 %. This finding demonstrates that having a chronic physical disease is a significant risk factor for comorbid MDD. Moreover, having a chronic physical disease and comorbid MDD is more likely to lead to the worst outcomes related to the disease state than is having any chronic disease (including MDD) alone or than is having any other combination of chronic diseases that does not include MDD [28].

We must thus consider the possibility of comorbid MDD in patients with chronic physical diseases. We cannot expect better outcomes by treating MDD and physical diseases in isolation.

# 3 Social Factors

## 3.1 Impairments in Physical and Social Functioning

According to the National Comorbidity Survey Replication Study conducted by face-to-face household survey of 9090 respondents [6], most patients who have had MDD for 12 months experience some impairment in their social functioning as a result of this condition [6]. Impairments related to social roles were the most common such outcome

(43.4 % severe or very severe), and those related to work roles were the least common (28.1 % severe or very severe) [6]. Patients with MDD for 12 months reported a mean of 35.2 days of work missed during the past year because of MDD [6]. Indeed, both physical and social functioning are impaired by MDD. Moreover, social functioning is significantly more impaired by MDD than it is by other chronic illness such as hypertension, diabetes and arthritis [29]. The degree of impairment in the domains of work, home, relationships and/or other social functions is closely related to the severity of the MDD [6].

## 3.2 Productivity and Economic Status

In the USA, 7.2 % of employees experience at least one depressive episode each year. Depressed individuals curtail their usual activities or stay in bed 66.4 days per year. It has been reported that depressed workers lose 27.2 work days per year and are responsible for a loss of US$36.6 billion salary-equivalent productivity dollars per year; this group is also responsible for US$27 billion in treatment costs [30]. Depressed workers report working at 70 % of their peak productivity [30].

In Japan, the estimated total cost related to depressive disorders (ICD-10: F32.0–F33.9) was ¥3,090,050 million (approximately US$38.8 billion) in 2008. The direct cost was ¥209,036 million (approximately US$2.63 billion).



Fig. 1 Costs of major depressive disorder in Japan a proportion of costs; b absolute costs, unit: Japanese Yen. Adapted from Wells et al. [29]
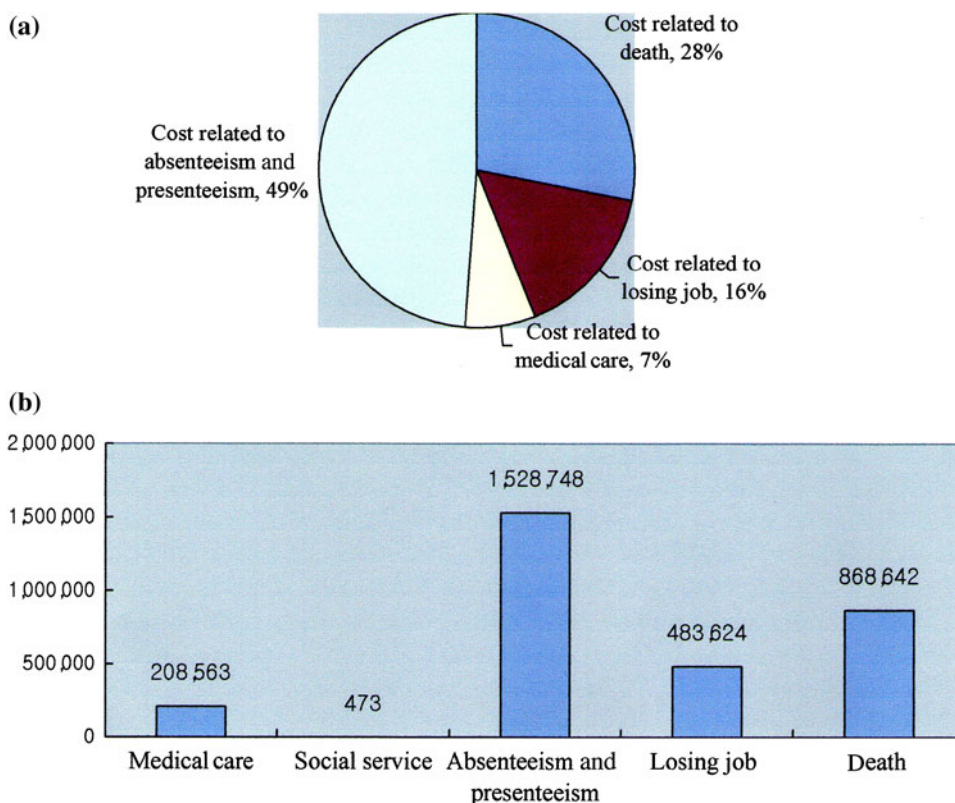
Considering absenteeism and presenteeism, an average of 68.7 days were lost to work, and the loss of productivity totalled ¥1,528,748 million (US$19.2 billion) (Fig. 1) [31].

MDD must be treated to restore the social and occupational functioning of patients with this disorder [32]. However, it is important that patients experience symptom remission, including improved cognition, before returning to work. Therefore, cognitive rehabilitation programmes are needed to enhance current treatment approaches to MDD.

Suicidality is also associated with MDD. Patients with major depression have a 2.2 % lifetime risk of suicide compared with a less than 0.05 % risk among those without this disorder, a 45-fold greater incidence [33].

## 4 Conclusions and Future Directions

Although MDD is common in east Asian countries, its prevalence has long been underestimated. One-third of patients with MDD meet the criteria for being considered treatment resistant. MDD is not only a mood disorder; it also entails physical disorders and disruption of social functioning. MDD exacerbates the physical symptoms associated with physical diseases, which may increase impairment in social functioning. Moreover, when comorbid with physical diseases, MDD can influence the outcomes of such diseases by leading to decreased treatment adherence and adverse health behaviours, which may increase mortality.

The treatment of physical symptoms increases the overall treatment response in MDD and the rate at which remission from this condition is achieved. Although MDD causes severe impairment in various domains of living, it is often difficult to identify these functional impairments in clinical settings. Each new episode of MDD tends to be more severe, longer, less responsive to treatment, and more likely to be followed by relapse as a result of a stressor. In addition, the interval between recurrences tends to become shorter [34].

Therefore, the optimal treatment for MDD should include collaboration focussed on comorbid physical diseases, rehabilitation aimed at restoring social functioning, and pharmacotherapy designed to ensure complete remission including psychological and physical symptoms as well as functional recovery.

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