A European Perspective on Depression in the Community: The DEPRES Study

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ABSTRACT

Depression is one of the most prevalent disorders in the general population, causing personal and social disability and impairment. Major studies assessing the diagnosis and management of depression have shown that it is often underdiagnosed and undertreated. A pan-European study aimed at assessing the extent and consequences of depression in six different countries is reported in this article. Different types of depressive profiles are analyzed and their respective management has been compared. The importance of improving diagnosis and treatment of depression is underlined. Appropriate management of depression depends on the recognition of depressive symptoms by patients, their possibility of seeking care, and the ability of the primary care physician to recognize the disorder and prescribe the appropriate medicines. Improvement in all of these fields is necessary.

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INTRODUCTION

Depression is one of the most prevalent and debilitating mental health disorders. It results in pain and suffering to individual patients and their families, as well as high costs to society at large. According to the international Global Burden of Disease study conducted by the World Bank,[1] depression is the fourth highest cause of disability in the world.

Using *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition and Third Edition-Revised criteria, several studies estimated the prevalence of depression in the general population across different countries in the world during the 1980s.[2-10] The 1-year prevalence of major depression was estimated to be as low as 0.6% in Taiwan[7] and as high as 10.3% in the United States (US).[9] Most studies reported the 1-year prevalence of major depression to be in the range of 3% to 7%. Similarly, the lifetime prevalence of major depression was lowest in Taiwan (0.9%)[7] and highest in France (16.6%)[10] and the US (17.1%).[9] Other studies reported the lifetime prevalence of depression to be in the range of 4.4% to 12.6%. In particular, the phase I Depression Research in European Society (DEPRES I) study of 78,463 subjects conducted in six European countries using questions from the Depression section of the Mini-International Neuropsychiatric Interview (MINI) found the average 6-month prevalence of depression to be 6.9%.[11] The lowest prevalence was reported in Germany at 3.8% and the highest prevalence was in the United Kingdom (UK) at 9.9%. In addition, in studies that have reported the prevalence of depression for women and for men, prevalence tends to be about 2-fold higher for women than it is for men.[11]

Variations in the estimates of prevalence of depression across studies are mostly related to methodological differences, including the instrument used, criteria used for the definition of depression, the extent of restrained probing for an episode of major depression, the study population, and cross-cultural variations in the expression and reporting of psychological symptoms related to depression. In general, studies in the US and Europe (particularly in France) tend to show a substantially higher prevalence of major depression. However, studies in Asia have reported the lowest prevalence of major depression.

An ongoing project conducted in six European countries (Belgium, France, Germany, the Netherlands, Spain, and the UK) using an adequate sample size and standardized methods of assessment is intended to produce up-to-date estimates of the prevalence of mental health disorders and, in particular, major depression in these countries. This project, the European Study of the Epidemiology of Mental Disorders, is similar in design to the World Health Organization's World Mental Health 2000 study, which aims to interview more than 100,000 people in 23 countries around the world. These studies, using a comparable design and standardized methods of assessment, will allow valid comparisons of international data on the prevalence of mental health disorders and, in particular, major depression in the general population.

A major set of issues on depression recently discussed in the literature is related to the underdiagnosis and undertreatment of major depression.[12] The Epidemiologic Catchment Area study reported that about a third of the patients suffering from an episode of major depression did not seek treatment and that overall, only 10% of patients with major depression were adequately treated.[13] The National Institute of Mental Health (NIMH) Collaborative Depression Study reported that, of 217 patients with major depression for at least 1 month, only 34% had received antidepressant therapy for at least 4 consecutive weeks, and in only 23% of patients could the treatment be considered adequate (150 mg of imipramine or

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its equivalent for 4 consecutive weeks).[14] The National Comorbidity Survey reported that, of subjects with a 1-year disorder, only 20% had sought any professional treatment.[15] Patients with more severe depression were more likely to seek care. However, only 35% of the most severely depressed patients sought treatment from their doctor.

Similarly, undertreatment of depression has been documented in the primary care setting. Katon and colleagues[16] found that, of 119 "distressed high utilizers of primary care services," 50% were depressed and required antidepressant treatment; however, only 10.7% received adequate treatment. The Medical Outcomes Study showed that only 24% of patients with major depression were receiving antidepressant therapy, and of the 24% only 15.8% of patients were receiving treatment from a general medical doctor.[17] As in community studies, patients with more severe forms of depression (mean of 18 symptoms of major depression, melancholia, or dysthymia in the preceding year reported on the baseline Diagnostic Interview Schedule) were more likely to receive antidepressant medication than those with a milder form of the illness (mean of 3 symptoms); 29.4% of patients with severe illness were receiving antidepressant medication as compared with 11.3% of patients with milder illness.

Even in the mental health sector, a high proportion of patients with depression are inadequately treated. In a medical records review of 201 inpatients with major depression, only 45% were receiving adequate antidepressant therapy.[18] The NIMH Collaborative Depression Study also showed substantial undertreatment of depression in the mental health sector; at the 2-year follow-up visit, only 49% of patients had received at least 200 mg of imipramine or its equivalent for 4 consecutive weeks.[19]

In the remainder of this article, we will focus on these issues. The results of two European studies, DEPRES I[11] and DEPRES II,[20] aimed at assessing the extent and consequences of underdiagnosis and undertreatment of major depressive syndromes will be briefly reported. The full reports of these studies have been previously published elsewhere.[11,20,21] These population-based studies were conducted in six European countries using a study population of approximately 80,000 subjects. Standardized methods of assessment and definition for depressive syndromes were used for the study. DEPRES I was conducted as the first phase of the study and intended to document the prevalence of depression in the community and assess the help-seeking process of depressed subjects and the treatment of depression. DEPRES II was the second phase of the study and included depressed patients who had consulted a healthcare professional for their symptoms, whether or not they had received any kind of treatment.

DEPRES I

DEPRES was a large European study set up to examine the prevalence of depression and assess its individual and social impact. It was conducted in Belgium, France, Germany, the Netherlands, Spain, and the UK. The study was conducted in two phases. DEPRES I had three main objectives: (1) to assess the 6-month prevalence of depression in the community, (2) determine the extent to which individuals suffering from depression sought treatment, and (3) assess the impact of depression among other variables and the number of working days lost. In DEPRES I, subjects were evaluated by the Depression section of the MINI in order to estimate the 6-month prevalence of depression. Questions concerning healthcare consultation, drug prescription, and days of work lost due to depression were also included.

The DEPRES I survey was based on house-to-house interviews with a demographically representative sample of adults in each participating country. In each country, the DEPRES interview was the second module in an omnibus market survey. The first module concerned consumer topics such as food products, magazine readership, and travel offers. It was judged that the maximum level of response to the screening questions for depression would be encouraged by placing the DEPRES interview second because the respondents would be familiar with the form of questioning and not too tired for active participation. The sample was designed to match the population in each country as closely as possible by taking account of gender, age, region, and other demographic factors such as employment. As a quality-control measure, there was a postal or telephone follow-up of a random sample of respondents within 2 weeks of interviews to verify the accuracy of responses. Interviews were conducted from April 1995–July 1995.

A total of 13,359 of the 78,463 adults who participated in the screening interviews were identified as suffering or having suffered from any type of depression in the previous 6 months; hence, the 6-month prevalence of any type of depression in the community was 17%. Three categories of depression were defined according to the number of symptoms and participant's perception of the impact on work and social activities: (1) major depression, (2) minor

TABLE 1. SIX-MONTH PREVALENCE OF DEPRESSION BY COUNTRY AND GENDER*

	% Prevalence (M/F)	
Country	Major Depression	Minor Depression
Belgium	5 (3.7/6.3)	1.5 (1.4/1.6)
France	9.1 (5.9/12.2)	1.7 (1.8/1.5)
Germany	3.8 (2.9/4.5)	1.9 (1.7/2.1)
Netherlands	6.9 (4.9/9.2)	3.0 (2.9/3.1)
Spain	6.2 (4.1/8.3)	1.5 (1.5/1.5)
United Kingdom	9.9 (8.2/11.2)	1.7 (2.1/1.5)
Total	6.9 (5/8.7)	1.8 (1.9/1.8)

M/F=male/female.

*Unweighted data; weighting the data by population size had no effect on the overall 6-month prevalence of 17%.

Adapted from Lépine JP et al.[11]

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depression, and (3) depressive symptoms. Major depression was defined as five or more symptoms that interfere substantially with work and social activities. Minor depression was defined as two to four symptoms that interfere substantially with work or social activities. Finally, the depressive symptoms category was defined as the presence of two or more symptoms that were not perceived to interfere substantially with work or social activities. Overall, in the six countries, 6.9% of the subjects suffered from major depression, 1.8% from minor depression, and another 8.3% had only depressive symptoms (Table 1).

The 6-month prevalence of major depression varied across countries participating in the survey, ranging from 3.8% in Germany to 9.1% in France and 9.9% in the UK. Major depression was more prevalent in women than in men in all six participating countries (8.7% versus 5% overall). The 6-month prevalence of major depression increased from 6.8% in subjects 24 years of age or younger to a maximum of 8.2% in those 45–54 years of age, and decreased thereafter with increase of age to 4.6% in subjects 75 years of age or older.

Forty-three percent of the survey's depressed subjects had failed to seek treatment for their symptoms and the majority (86%) had not even considered consulting a medical specialist. Among the depressed subjects who did seek treatment for their symptoms, those with more severe depression were more likely to do so. However, even among those fulfilling our criteria for major depression, 31% had failed to visit a physician and generally had not even considered seeking medical help. The primary care physician was the medical specialist most frequently consulted by depressed subjects in every country. Only 9% of depressed subjects had consulted a psychiatrist and fewer than 10% had seen a psychologist or counselor except in the Netherlands, where 19.5% of patients had consulted a psychologist or counselor.

There appeared to be a correlation between the severity of depression and the overall use of health services. Major depression imposed the greatest demand on primary care resources in every country. Overall, persons suffering from major depression made almost three times as many visits to their general practitioner or family doctor during the previous 6 months as compared with persons not suffering from depression (4.4 visits versus 1.5 visits).

More than two thirds of depressed subjects (69%) received no drug therapy for their symptoms (Table 2). Given that most healthcare consultations were made by subjects with the most severe and disabling depressive symptoms, it is striking that 59% of the patients meeting our criteria for a diagnosis of major depression were not prescribed any form of treatment.

Overall, 25% of depressed subjects taking a medication were receiving antidepressant therapy; hence, only about 8% of all depressed subjects were receiving antidepressant therapy. There was widespread use of tranquilizers, and with the exception of Germany and the UK, more depressed subjects were taking tranquilizers than antidepressant drugs. The only country in which antidepressants were prescribed significantly more frequently than tranquilizers was the UK (31% versus 8%). By far, most of the tranquilizers used were benzodiazepines.

Depressed subjects in each country took more sick days due to any illness during the previous 6 months than nonsufferers. There was a strong correlation between the severity of depression and the number of work days lost (Figure).

Major depression had the greatest impact on productivity, with sufferers losing four times as many working days over 6 months as nonsufferers (13 days versus 3 days). In addition, in each country there was an inverse correlation between the severity of depression and whether depressed subjects were in paid employment.

DEPRES II

During the second phase of the study (DEPRES II), participants in DEPRES I were eligible to take part in detailed interviews if (1) they had suffered from depression (major or minor depression or depressive symptoms) during the previous 6 months, (2) they had consulted a healthcare professional about their symptoms during the previous 6 months, and (3) they were willing to participate. The main objectives of this second phase were to obtain information about the medical management, treatment needs, and expectations of prescribed medications of depressed adults who present to healthcare professionals.

DEPRES II interviews were conducted face-to-face within 3 weeks of DEPRES I screenings. The interviews were based on a semistructured instrument which included

TABLE 2. PRESCRIPTION OF MEDICATION AND SEVERITY OF DEPRESSION

	% Prescription of Any Kind of Drug			
Country	All Depression	Major Depression	Minor Depression	Depressive Symptoms
Belgium	38.8	49.9	36.7	29.6
France	38.7	51.4	29.2	30.0
Germany	22.6	34.6	26.1	13.3
Netherlands	37.9	50.8	38.1	24.1
Spain	26.9	34.5	18.9	22.7
United Kingdom	25.4	34.6	22.8	17.0
Total	30.7	41.4	27.7	22.5

Adapted from Lépine JP et al.[11]

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78 questions on duration and symptoms of depression, optimism about the future, consultation with healthcare professionals, disruption of normal life and employment, expectations of prescribed medication, and current management of depression. The response rate among DEPRES I participants who met the eligibility criteria for DEPRES II was 53%. There were slight differences in the response rate among countries (49%–61%).

A total of 1,884 subjects participated in DEPRES II. Approximately half of the subjects were younger than 45 years of age and 30% were younger than 35 years of age. The majority of subjects were female (70%) and most respondents lived in urban or suburban areas. Thirty-eight percent were employed, 57% owned their place of residence, and 77% had children. Below, we present a summary of the results of the study on (1) duration and symptoms of depression, (2) optimism about the future, (3) consultation with healthcare professionals, (4) disruption to normal life and employment, (5) expectations of prescribed medication, and (6) current management of depression.

Duration and Symptoms

The most commonly reported symptoms of depression were low mood (76%), fatigue (73%), and sleep problems (63%). More than half of the patients had felt anxious (57%) and 34% had felt that life was not worth living. "Anhedonia," as such, was not assessed in the study. On the other hand, less interest in hobbies, friends, and acquaintances was reported in 37% of the respondents. The average time from depression onset was 45 months; 43% of the respondents had suffered from depression for more than 5 years. Forty-one percent of the participants reported experiencing relief from their symptoms of depression for periods of longer than 6 months. The rate of current depression was 58%. The most frequently given reasons for the current or latest period of depression were stress (36%), own physical illness (33%), or problems with friends or family members (31%). Approximately two thirds of the respondents had experienced a concomitant medical illness during their current or latest period of depression; the most frequently reported medical problems were backache (21%), abnormal blood pressure (18%), heart problems (11%), migraine (11%), and arthritis (10%).

Optimism About the Future

Forty-three percent of the study participants reported that they thought they would never recover from depression. This lack of optimism about their future prospects was most commonly linked to the belief that their social or family problems (38%) or their physical illness (33%) would not improve.

Consultation With Healthcare Professionals

By far, the majority of respondents (90%) had consulted a general practitioner for their symptoms of depression. In addition, 19% of the participants had consulted a psychiatrist or a neurologist and 17% had consulted a psychologist, psychotherapist, or counselor. Most respondents (79%) found professional counseling helpful.

Disruptions to Normal Life and Employment

Several aspects of normal life including sleep, general health, marriage or personal relationships, the ability to work, and optimism about the future had been adversely affected by depression. Respondents reported that they had been unable to participate in normal activities for an average of 30 days and had lost an average of 20 days of work during the 6-month period preceding the interview due to their depression.

Expectations of Prescribed Medication

Respondents expressed the following to be the most important desirable characteristics of their medication: that it would not cause daytime drowsiness (60%), it would allow normal sleep (58%), it would make one feel like one's normal self (54%), it would not affect concentration (44%), and it would reduce feelings of depression in a few days (44%).

CURRENT MANAGEMENT OF DEPRESSION

During their latest period of depression, a medication had been prescribed to 53% of the respondents for phase II. Approximately a third had received an antidepressant (30%), most frequently a tricyclic antidepressant (TCA) (15%) or a selective serotonin reuptake inhibitor (SSRI) (14%). More than two thirds of the respondents (70%) had not received any antidepressant therapy. Prescription of benzodiazepines alone was fairly common (28% of the prescriptions for depression). A significantly higher proportion of respondents who had been prescribed an SSRI reported that the medication made them feel more like their normal self than those give a TCA, and a lower proportion reported concentration lapses, weight problems, and heavy-headedness.

Finally, cluster analysis was done in order to identify depressed patient types who present to healthcare professionals.[21] Cluster analysis is a multivariate procedure designed to group individuals into clusters or "types" with high internal homogeneity and high external heterogeneity based on a set of defining factors. Prior to the cluster analy-

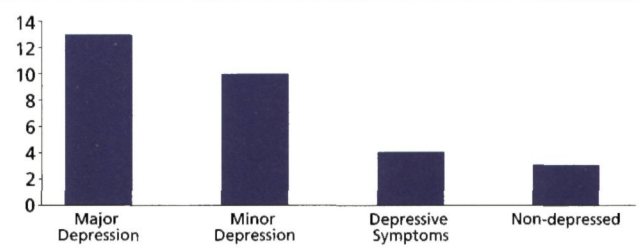

FIGURE. Relationship between severity of depression and work days lost due to illness during the previous 6 months.

Adapted from Lépine JP et al.[11]

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sis, a factor analysis was done to derive an appropriate set of defining factors. Data for the 1,884 DEPRES II respondents were used for this set of analyses.

Specifically, the aim of the cluster analysis was to define the types of depressed patients who present to healthcare professionals based on attributes related to the nature of depression (eg, causes, duration, and symptoms), rather than its outcomes (eg, consultation with healthcare professionals and management).

A six-cluster solution was considered as optimal to group the subjects who participated in DEPRES II into (1) moderately impaired depression, (2) depression associated with chronic physical problems, (3) severe depression associated with anxiety, (4) depression associated with social problems, (5) depression associated with sleep problems, and (6) depression associated with tiredness or fatigue (Table 3). No patient type was dominant; the proportion of DEPRES II respondents in each of the patient types ranged from 10% to 26%.

Patients in cluster I (moderately impaired depression) were the least severely affected in terms of symptoms and disruption to normal life and employment. Patients with moderately impaired depression who were in paid employment had lost an average of 6 days of work during a 6-month period. Seventy percent of patients in cluster I were optimistic about recovery from depression. The proportions of patients who had consulted a psychiatrist (13%) or a psychologist, psychotherapist, or counselor (11%) were lower than in any other patient type. Depression tended to be episodic: 55% of the patients with moderately impaired depression had experienced periods of longer than 6 months when they had been free from depression.

Eighty percent of patients belonging to cluster II (depression associated with chronic physical problems) had concomitant medical conditions (abnormal blood pressure, 28%; backache, 26%; arthritis, 19%; heart problems, 17%). Depression was usually chronic; the mean time from onset was 55 months and almost all the subjects were pessimistic about recovering from depression. Approximately one third of the patients were under the care of a nonpsychiatry-related specialist for their depression. Patients with depression associated with chronic physical problems lost an average of 22 days of work in a 6-month period.

The third cluster was characterized by severe depression associated with anxiety. Eighty-six percent of this group was suffering from feelings of anxiety, panic, and suicidal ideation. Even though depression was severe in this group, patients belonging to cluster III were more optimistic about recovering from depression than patients suffering from depression associated with chronic physical problems (cluster II). Twenty-seven percent of the subjects were consulting a psychiatrist and another 27% had consultation with a psychologist, psychotherapist, or counselor during the previous 6 months. Patients in this cluster lost an average of 30 working days due to depression during the previous 6 months.

Cluster IV represented patients suffering from depression associated with social problems. The reason for the onset of the most recent depressive period appeared to be financial and relationship difficulties. Patients in this cluster were more likely to be divorced or separated than average (24% versus 14% overall), to have three or more children (36% versus 29% overall), and to live in a rented accommodation (50% versus 41% overall). Half of the patients reported feeling worthless or inadequate, and suicidal ideation was common. The mean duration of the first depressive period was longer than in any other patient type (56 months). The overwhelming majority of

TABLE 3.
MANIFESTATIONS OF DEPRESSION ACCORDING TO THE RESULTS OBTAINED FROM CLUSTER ANALYSIS

Cluster	Descriptive Titles	Main Characteristics	Number of Patients
I	Moderately impaired depression	• Least severely affected • Average of 6 days of work lost in a 6-month period • Lower rate of healthcare consultations	323
II	*Depression associated with chronic physical problems*	• *Chronic depression* • 1/3 of the patients under the care of a non–psychiatry-related specialist • Average of 22 days of work lost in a 6-month period	305
III	Severe depression associated with anxiety	• 27% had consulted a psychiatrist during the previous 6 months • Average of 30 days of work lost in a 6-month period	347
IV	Depression associated with social problems	• More likely to be divorced or separated • Frequencies of consultations and disruptions to paid employment approximately equal to the overall average for clusters combined	182
V	Depression associated with sleep problems	• Patients similar for most attributes	475
VI	Depression associated with tiredness or fatigue	• Close to average on most attributes	252

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the patients (90%) were pessimistic about recovering from depression. The frequencies of consultations with healthcare professionals and disruptions to paid employment were comparable to those in other clusters.

Patients suffering from depression with sleep problems and from depression associated with fatigue were classified in clusters V and VI, respectively. Furthermore, patients in these two clusters were similar for most attributes but the factor differentiating them was the ability to sleep normally. Patients in these two clusters were close to the average on most attributes. The mean time of depression onset was 33 months in cluster V and 35 months in cluster VI.

Depression management was assessed in each cluster. Prescription of antidepressants was highest in patients with severe depression associated with anxiety. However, even in this group, 57% had not been prescribed an antidepressant and 15% had received only benzodiazepines. Prescription of antidepressants was lowest in patients with moderately impaired depression (19%). Twenty-six percent of patients in this cluster had received a tranquilizer and 20% had received only benzodiazepines. Prescription of antidepressants for patients with depression associated with physical problems, social problems, and fatigue was similar to that in the overall DEPRES II population (30%).

Prescription of tranquilizers (mostly benzodiazepines) for patients with depression associated with physical problems was similar to the average prescription rate for tranquilizers in the overall DEPRES II population. However, patients older than 64 years of age and those who were unemployed were more likely to receive a tranquilizer than younger and employed patients. Patients with depression associated with sleep problems were more likely to receive a tranquilizer (28%), usually a benzodiazepine (18%), than those with depression associated with tiredness and fatigue (21% total; 11% benzodiazepine alone).

DISCUSSION

In summary, DEPRES was a large, in-depth European survey of depression in the community, which provided an opportunity to identify depressed patients, their treatment needs, and consequences of depression for individuals and society at large. In the first phase of the study (DEPRES I), the 6-month prevalence of any type of depression in the community was shown to be 17%, while 6.9% of patients were suffering from major depression. In addition, there were substantial variations in the prevalence of depression across countries in Europe. Possible reasons for cross-country differences in the prevalence of depression include differences in age and gender distribution, cultural differences in expression of depression symptoms, and the fact that assessment of depression symptoms using various instruments yields different results across countries.

A substantial proportion (43%) of patients suffering from depression did not seek any treatment. Most of the patients who did seek care consulted a primary care physician. Patients with more severe depression were more likely to seek care. However, even among those suffering from major depression, 31% had failed to visit a physician. Compared with subjects who were not depressed, those with major depression lost four times as many working days over a 6-month period.

Approximately 70% of the depressed patients who presented to a healthcare professional did not receive any medication for their symptoms. Given that most healthcare consultations were made by subjects with the most severe and disabling depressive symptoms, it is striking that 59% of the patients suffering from major depression were not prescribed any form of treatment. Overall, 25% of depressed subjects taking a medication were receiving antidepressant therapy; hence, only about 8% of all depressed subjects received an antidepressant. There was a widespread use of tranquilizers and, in most countries, more depressed subjects were prescribed tranquilizers than antidepressants.

In the second phase of the study (DEPRES II), detailed interviews were conducted with 1,884 DEPRES I subjects who had consulted a healthcare professional about their symptoms during the previous 6 months. The average time from onset of depression was 45 months and the most commonly experienced symptoms were low mood, tiredness, and sleep problems. Respondents had not been able to participate in normal activities for an average of 30 days in the previous 6 months and, on average, 20 days of work had been lost during the latest period of depression. Overall, about 30% of patients who had sought care received an antidepressant. Those who received a SSRI were more likely to report that their treatment made them feel like their normal self as compared with those prescribed a TCA; patients who had been prescribed a SSRI were also less likely to report side effects.

A cluster analysis of the data in DEPRES II identified six types of depressed patients. Patients with moderately impaired depression had episodic depression and lesser disability. Depression associated with chronic physical problems and depression associated with social problems are characterized by chronic physical illness and relationship or financial difficulties, respectively. Sufferers from these two types of depression are often pessimistic about recovery. Depression associated with sleep problems is accompanied by symptoms of tiredness and broken or inadequate sleep, and is often caused by stress. Tiredness is the principal symptom of depression associated with fatigue; however, sleep is unaffected. Finally, severe depression associated with anxiety commonly presents with chronic symptoms, including anxiety and panic, and is highly disruptive to normal life and employment. All patient types would benefit from antidepressant therapy.

In addition to documenting the prevalence of depression and its socioeconomic impact in the community, results of DEPRES I and II underscore the under-recognition and undertreatment of depression. The findings of the DEPRES study in this regard are in broad agreement with previous studies, which have shown that underdiagnosis and undertreatment of depression occur frequently despite the fact that appropriate

screening tools and effective treatments exist for depression. Several studies have documented the substantial extent to which depression goes unrecognized and untreated in the community, primary care setting, and mental health sector.[12]

Underdiagnosis and undertreatment of depression are related to provider, patient, and healthcare system factors.[12] Physicians are often not adequately trained to properly diagnose and manage patients with depression. There also appears to be lack of sufficient concern for depression as a "real disease." In addition, diagnosis and proper management of depression can be time consuming and there might be too little time available in the primary care setting to manage depressed patients effectively.

Patients themselves often do not realize that they are suffering from depression. Because of depression, patients also often lack sufficient drive and the will to seek treatment. Stigma remains an issue that also hinders the patient from seeking help. Noncompliance rates are high because of a delay in onset of effects, the need to continue treatment after the initial response, and failure to warn about side effects.

Health systems have often viewed depression as an episodic problem and have not put in place the appropriate management systems for the chronic and recurrent nature of the disorder. In particular, in the US, frequent monitoring of patients has been discouraged through reimbursement policies. In general, many health insurance and managed care companies have not provided adequate coverage for mental health consultations, and reimbursement is often not given if patients require more than one treatment approach or referral to more than one specialist.

In conclusion, we showed in this pan-European study that depression is a prevalent, underdiagnosed, and undertreated illness. These results are consistent with those obtained in several other studies conducted in different countries across the world. In addition, results of the cluster analysis showed that depression can present with several types of manifestations and that this varied expression can in part explain the difficulties in diagnosis and effective treatment of depression. Our study results also underscore the importance of assessing the degree of impairment related to depression. Underdiagnosis and undertreatment of depression result in suffering for patients and substantial costs for society.

Recently, results of a cost-benefit analysis showed that the savings that would be realized by appropriately treating people with affective disorders would outweigh treatment costs by about $4 billion a year in the US.[22] Appropriate screening tools and effective treatments are available for depression. Primary care physicians play a key role in the recognition and treatment of depression. More efforts are needed to improve the training of primary care physicians in the diagnosis and management of the condition. Healthcare systems need to more effectively accommodate the chronic and recurrent nature of depression. CNS

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MYOBLOC™
BOTULINUM TOXIN TYPE B
INJECTABLE SOLUTION

DESCRIPTION

MYOBLOC™ (Botulinum Toxin Type B) Injectable Solution is a sterile liquid formulation of a purified neurotoxin that acts at the neuromuscular junction to produce flaccid paralysis. The neurotoxin is produced by fermentation of the bacterium *Clostridium botulinum* type B (Bean strain) and exists in noncovalent association with hemagglutinin and nonhemagglutinin proteins as a neurotoxin complex. The neurotoxin complex is recovered from the fermentation process and purified through a series of precipitation and chromatography steps.

MYOBLOC™ is provided as a clear and colorless to light yellow sterile injectable solution in 3.5-mL glass vials. Each single use vial of formulated MYOBLOC™ contains 5000 U of Botulinum Toxin Type B per milliliter in 0.05% human serum albumin, 0.01 M sodium succinate, and 0.1 M sodium chloride at approximately pH 5.6.

One unit of MYOBLOC™ corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. The method for performing the assay is specific to Elan Pharmaceutical's manufacture of MYOBLOC™. Due to differences in specific details such as the vehicle, dilution scheme and laboratory protocols for various mouse LD50 assays, Units of biological activity of MYOBLOC™ cannot be compared to or converted into units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal dose-activity relationships to human dose estimates. The specific activity of MYOBLOC™ ranges between 70 to 130 U/ng.

INDICATIONS AND USAGE

MYOBLOC™ is indicated for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

CONTRAINDICATIONS

MYOBLOC™ is contraindicated in patients with a known hypersensitivity to any ingredient in the formulation.

WARNINGS

Do not exceed the doses of MYOBLOC™, described under Dosage and Administration. Risks resulting from administration at higher doses are not known.

Caution should be exercised when administering MYOBLOC™ to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of MYOBLOC™. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some cases, dysphagia has lasted months and required placement of a gastric feeding tube.

There were no documented cases of botulism resulting from the IM injection of MYOBLOC™ in patients with CD treated in clinical trials. If, however, botulism is clinically suspected, hospitalization for the monitoring of systemic weakness or paralysis and respiratory function (incipient respiratory failure) may be required.

Dysphagia is a commonly reported adverse event following treatment with all botulinum toxins in cervical dystonia patients. In the medical literature, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

Only 9 subjects without a prior history of tolerating injections of type A botulinum toxin have been studied. Treatment of botulinum toxin naive patients should be initiated at lower doses of MYOBLOC™ (see Adverse Reactions: Overview).

DRUG INTERACTIONS

Co-administration of MYOBLOC™ and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes at the same time or within less than 4 months of each other is unknown. However, neuromuscular paralysis may be potentiated by co-administration or overlapping administration of different botulinum toxin serotypes.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No long-term carcinogenicity studies in animals have been performed.

PREGNANCY

PREGNANCY CATEGORY C. Animal reproduction studies have not been conducted with MYOBLOC™. It is also not known whether MYOBLOC™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. MYOBLOC™ should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MYOBLOC™ is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

In the controlled studies summarized in CLINICAL STUDIES, for MYOBLOC™ treated patients, 152 (74.5%) were under the age of 65, and 52 (25.5%) were aged 65 or greater. For these age groups, the most frequent reported adverse events occurred at similar rates in both age groups. Efficacy results did not suggest any large differences between these age groups. Very few patients aged 75 or greater were enrolled, therefore no conclusions regarding the safety and efficacy of MYOBLOC™ within this age group can be determined.

ADVERSE REACTIONS

Overview

The most commonly reported adverse events associated with MYOBLOC™ treatment in all studies were dry mouth, dysphagia, dyspepsia, and injection site pain. Dry mouth and dysphagia were the adverse reactions most frequently resulting in discontinuation of treatment. There was an increased incidence of dysphagia with increased dose in the sternocleidomastoid muscle. The incidence of dry mouth showed some dose-related increase with doses injected into the splenius capitis, trapezius and sternocleidomastoid muscles.

Only nine subjects without a prior history of tolerating injections of type A botulinum toxin have been studied. Adverse event rates have not been adequately evaluated in these patients, and may be higher than those described in Table 1.

Discussion

Adverse reaction rates observed in the clinical trials for a product cannot be directly compared to rates in clinical trials for another product and may not reflect the rates observed in actual clinical practice. However, adverse reaction information from clinical trials does provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

MYOBLOC™ was studied in both placebo controlled single treatment studies and uncontrolled repeated treatment studies; most treatment sessions and patients were in the uncontrolled studies. The data described below reflect exposure to MYOBLOC™ at varying doses in 570 subjects, including more than 300 patients with 4 or more treatment sessions. Most treatment sessions were at doses of 12500 U or less. There were 57 patients administered a dose of 20000 or 25000 U. All but nine patients had a prior history of receiving Type A botulinum toxin and adequately tolerating the treatment to have received repeated doses.

The rates of adverse events and association with MYOBLOC™ are best assessed in the results from the placebo controlled studies of a single treatment session with active monitoring. The data in Table 1 reflect those adverse events occurring in at least 5% of patients exposed to MYOBLOC™ treatment in pooled placebo controlled clinical trials. Annual rates of adverse events are higher in the overall data which includes longer duration follow-up of patients with repeated treatment experience. The mean age of the population in these studies was 55 years old with approximately 66% being female. Most of the patients studied were Caucasian and all had cervical dystonia that was rated as moderate to severe in severity.

Table 1 - Treatment-Emergent AEs Reported by at Least 5% of MYOBLOC™ Treated Patients by Dose Group, Following Single Treatment Session in Controlled Studies -09,-301 and-302

	Dosing Groups			
Adverse Event (COSTART Term)	Placebo (N=104)	2500 U (N=31)	5000 U (N=67)	10,000 U (N=106)
Dry Mouth	3 (3%)	1 (3%)	8 (12%)	36 (34%)
Dysphagia	3 (3%)	5 (16%)	7 (10%)	27 (25%)
Neck Pain related to CD[a]	17 (16%)	0 (0%)[b]	11 (16%)	18 (17%)
Injection Site Pain	9 (9%)	5 (16%)	8 (12%)	16 (15%)
Infection	16 (15%)	4 (13%)	13 (19%)	16 (15%)
Pain	10 (10%)	2 (6%)	4 (6%)	14 (13%)
Headache	8 (8%)	3 (10%)	11 (16%)	12 (11%)
Dyspepsia	5 (5%)	1 (3%)	0 (0%)	11 (10%)
Nausea	5 (5%)	3 (10%)	2 (3%)	9 (8%)
Flu Syndrome	4 (4%)	2 (6%)	6 (9%)	9 (8%)
Torticollis	7 (7%)	0 (0%)	3 (4%)	9 (8%)
Pain Related to CD/Torticollis	4 (4%)	3 (10%)	3 (4%)	7 (7%)
Arthralgia	5 (5%)	0 (0%)	1 (1%)	7 (7%)
Back Pain	3 (3%)	1 (3%)	3 (4%)	7 (7%)
Cough Increased	3 (3%)	1 (3%)	4 (6%)	7 (7%)
Myasthenia	3 (3%)	1 (3%)	3 (4%)	6 (6%)
Asthenia	4 (4%)	1 (3%)	0 (0%)	6 (6%)
Dizziness	2 (2%)	1 (3%)	2 (3%)	6 (6%)
Accidental Injury	4 (4%)	0 (0%)	3 (4%)	5 (5%)
Rhinitis	6 (6%)	1 (3%)	1 (1%)	5 (5%)

[a] Not a COSTART term
[b] Not collected in Study –09 by special COSTART term

In the overall clinical trial experience with MYOBLOC™ (570 patients, including the uncontrolled studies), most cases of dry mouth or dysphagia were reported as mild or moderate in severity. Severe dysphagia was reported by 3% of patients, none of these requiring medical intervention. Severe dry mouth was reported by 6% of patients. Dysphagia and dry mouth were the most frequent adverse events reported as a reason for discontinuation from repeated treatment studies. These adverse events led to discontinuation from further treatments with MYOBLOC™ in some patients even when not reported as severe.

The following additional adverse events were reported in 2% or greater of patients participating in any of the clinical studies (COSTART terms, by body system):

Body as a Whole: allergic reaction, fever, headache related to injection, chest pain, chills, hernia, malaise, abscess, cyst, neoplasm, viral infection; Musculoskeletal: arthritis, joint disorder; Cardiovascular System: migraine; Respiratory: dyspnea, lung disorder, pneumonia; Nervous System: anxiety, tremor, hyperesthesia, somnolence, confusion, pain related to CD/torticollis, vertigo, vasodilation; Digestive System: gastrointestinal disorder, vomiting, glossitis, stomatitis, tooth disorder; Skin and Appendages: pruritis; Urogenital System: urinary tract infection, cystitis, vaginal moniliasis; Special Senses: amblyopia, otitis media, abnormal vision, taste perversion, tinnitus; Metabolic and Nutritional Disorders: peripheral edema, edema, hypercholesterolemia; Hemic and Lymphatic System: ecchymosis.

Immunogenicity

A two stage assay was used to test for immunogenicity and neutralizing activity induced by treatment with MYOBLOC™. In order to account for varying lengths of follow-up, life-table analysis methods were used to estimate the rates of development of immune responses and neutralizing activity. During the repeated treatment studies, 446 subjects were followed with periodic ELISA based evaluations for development of antibody responses against MYOBLOC™. Only patients who showed a positive ELISA assay were subsequently tested for the presence of neutralizing activity against MYOBLOC™ in the mouse neutralization assay (MNA). 12% of patients had positive ELISA assays at baseline. Patients began to develop new ELISA responses after a single treatment session with MYOBLOC™. By six months after initiating treatment, estimates for ELISA positive rate were 20%, which continued to rise to 36% at one year and 50% positive ELISA status at 18 months. Serum neutralizing activity was primarily not seen in patients until after 6 months. Estimated rates of development were 10% at one year and 18% at 18 months in the overall group of patients, based on analysis of samples from ELISA positive individuals. The effect of conversion to ELISA or MNA positive status on efficacy was not evaluated in these studies, and the clinical significance of development of antibodies has not been determined.

The data reflect the percentage of patients whose test results were considered positive for antibodies to MYOBLOC™ in both an *in vitro* and *in vivo* assay. The results of these antibody tests are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to MYOBLOC™ with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

Symptoms of overdose are likely not to present immediately following injection(s). Should a patient ingest the product or be accidentally overdosed, they should be monitored for up to several weeks for signs and symptoms of systemic weakness or paralysis.

In the event of an overdose an antitoxin may be adminstered. Contact Elan Pharmaceuticals at 1-888-638-7605 for additional information and your State Health Department to process a request for antitoxin through the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration.

HOW SUPPLIED

MYOBLOC™ is available in the following three presentations.

Dosage Strength	Volume Per Vial	Single-Vial Carton
2500 U	0.5 mL	NDC 59075-710-10
5000 U	1.0 mL	NDC 59075-711-10
10,000 U	2.0 mL	NDC 59075-712-10

Store under refrigeration at 2°- 8°C (36°- 46°F). **DO NOT FREEZE. DO NOT SHAKE.**

élan pharmaceuticals
Manufactured by Elan Pharmaceuticals, Inc., South San Francisco, CA 94080

701330 Rev. 12/00

References: 1. Brashear A, Lew MF, Dykstra DD, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. *Neurology.* 1999;53:1439-1446. **2.** Brin MF, Lew MF, Adler CH, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology.*1999;53:1431-1438. **3.** Myobloc Prescribing Information. South San Francisco, CA: Elan Pharmaceuticals.

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