

Clara Grosso *Editor*

Herbal Medicine in Depression

Traditional Medicine to Innovative Drug
Delivery

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Preface

This book was conceived by professionals and researchers from different backgrounds, combining ethnopharmacology, phytochemistry, pharmacology and neuroscience topics, for a better understanding of depression. According to the World Health Organization, more than 350 million people of all ages suffer from depression, and the existing drug therapies are only suitable to treat ca. 60–70 % of patients. Therefore, this book intends to debate the current knowledge on the aetiology of depression, the mechanism of action of the available antidepressants and what routes should be followed to pursue more efficient tools for treatment-resistant patients.

This book starts with a general chapter (Chap. 1) dealing with aspects of prevalence and costs of the disease worldwide as well as the theories postulated since the 1950s to explain the pathophysiology of depression. The reader will understand that in the light of nowadays knowledge a unified hypothesis of depression is not sustained due to its multifactorial features.

Chapter 2 summarizes the mechanism of action of the antidepressant drugs available to treat depression, as well as possible new targets to take into account in new drug discovery programs.

Chapters 3 and 4 highlight the importance that cellular and animal models have had in our understanding of the pathophysiology of depression. A critical analysis of the advantages and disadvantages of each model is also presented.

Since ancient times, nature has been a rich source of drugs which display higher structural diversity than the synthetic ones. With this in mind and being aware that sooner or later new antidepressant drugs have to be tested, approved and released, big pharma companies are encouraged to create new programs of drug discoveries based on natural products. Therefore, several medicinal plants with antidepressant activity were compiled in Chaps. 5–10, aiming at contributing (a) to gather the traditional knowledge of communities transferred orally from generation to generation or already established in traditional medicines and (b) to arouse the interest of the most skeptical persons. These chapters will stimulate readers to appreciate the benefits of natural products on human health.

In a more alternative and futuristic view to treat depression, new drug delivery systems for antidepressant drugs are described in detail in Chap. 11.

Finally, Chap. 12 takes into account all the issues discussed over the previous chapters and proposes new strategies that can be followed to reduce the burden of depression in societies around the world.

I sincerely hope the readers will enjoy and learn from the contents of this book.

Porto, Portugal

Clara Grosso

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Chapter 1

Depressive Disorders: Prevalence, Costs, and Theories

Clara Grosso, Patrícia Valentão, and Paula B. Andrade

Abstract The estimated global cost of mental health conditions, including depressive disorders, was US\$2.5 trillion in 2010. According to the World Health Organization (WHO), more than 350 million people of all ages suffer from depression, 10–40 % of them not improving their condition with the current drug therapies, thus contributing to the increased burden of mental disorders. Indeed, prognostics are not encouraging since it is predicted that unipolar depressive disorders will be the first cause of disability-adjusted life years (DALYs) by the year 2030. For these reasons, it is urgent to find new antidepressant drugs that act on other targets rather than the conventional one (monoamine transmission). Having this in mind, this chapter provides a critical review of the theories available to explain the pathogenesis of depressive disorders, namely, those focusing on disturbances of monoamine, glutamate and GABA transmission, changes in the hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammation, neurogenesis and neurotrophic factors, glial pathology, epigenetic mechanisms, and disturbance of the circadian rhythm.

Keywords Neurotransmitters • Neuroinflammation • Hypothalamic-pituitary-adrenal axis • Neuroplasticity • Epigenetics • Glial cells • Circadian rhythm

1.1 Introduction

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* considers two separate branches on the mood disorder diagnostic tree: (1) depressive disorders, comprising disruptive mood dysregulation disorder, major

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depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder, and (2) bipolar and related disorders, including bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder (American Psychiatric Association 2013).

An approach to these branches is provided below.

1.1.1 Depressive Disorders

Disruptive mood dysregulation disorder (DMDD) is characterized by severe and recurrent temper outbursts that are grossly out of proportion in intensity or duration to the situation. On average, these occur three or more times per week for 1 year or more. Between outbursts, children with DMDD display persistently irritable or angry mood, most of the day and nearly every day. The diagnostic requires the above symptoms to be present in at least two settings (at home, at school, or with peers) for 12 or more months, and symptoms must be severe in at least one of these settings. The onset of symptoms must be before the age of 10, and DMDD diagnostic should not be made for the first time before the age of 6 or after the age of 18 (American Psychiatric Association 2013).

Major depressive disorder (MDD) is characterized by five or more of the following nine symptoms during 2 weeks: (1) depressed mood, (2) loss of interest or pleasure, (3) change of weight (5 % change over 1 month) or appetite, (4) insomnia or hypersomnia, (5) psychomotor retardation or agitation, (6) loss of energy or fatigue, (7) worthlessness or guilt, (8) impaired concentration or indecisiveness, and (9) thoughts of death or suicidal ideation or attempt. From these symptoms, at least (1) and (2) are always present (Uher et al. 2014; American Psychiatric Association 2013).

Persistent depressive disorder (dysthymia) is characterized by depressed mood for the most of the day, for more days than not, for 2 years or longer. The diagnostic requires the presence of two or more of the following symptoms during the same period and never without symptoms for more than 2 months: (1) poor appetite or overeating, (2) insomnia or hypersomnia, (3) low energy or fatigue, (4) low self-esteem, (5) impaired concentration or indecisiveness, and (6) hopelessness (Uher et al. 2014; American Psychiatric Association 2013).

Premenstrual dysphoric disorder is characterized by the presence of five (out of eleven) symptoms in the week before menstruation, the symptoms starting to disappear few days after the beginning of menstruation and vanishing completely in the week after. The presence of, at least, one of the following symptoms is characteristic: (1) marked affective lability (e.g., suddenly feeling sad or tearful or experiencing increased sensitivity to rejection); (2) persistent and marked anger or irritability or increased interpersonal conflicts; (3) marked depressed mood, feeling of

hopelessness, or self-deprecating thoughts; and (4) marked anxiety, tension, feelings of being “keyed up” or “on the edge.” Additionally, one or more of the following symptoms are also present:

1. Decreased interest in common activities (e.g., work, school, friends, and hobbies)
2. Subjective sense of difficulty in concentrating
3. Lethargy, easy fatigability, or marked lack of energy
4. Marked change in appetite, overeating, or specific food cravings
5. Hypersomnia or insomnia
6. Subjective sense of being overwhelmed or out of control
7. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, sensation of bloating, or weight gain (American Psychiatric Association 2013)

Substance-/medication-induced depressive disorder is a prominent and persistent disturbance of mood or loss of interest or pleasure as a direct physiological consequence of a drug of abuse, a medication, another somatic treatment for depression, or toxin exposure (American Psychiatric Association 2013).

A mood disorder due to another medical condition is characterized by a prominent and persistent disturbance of mood or loss of interest or pleasure as a direct physiological consequence of another medical condition (American Psychiatric Association 2013).

Other specified depressive disorders and unspecified depressive disorders are those with features that do not meet criteria for specified depressive disorders. For the first group, the clinician chooses to communicate the specific reason why the presentation does not meet criteria for any specific depressive disorder, while in the second one, he does not specify. Other specified depressive disorder class includes recurrent brief depression, brief depressive episode (4–13 days), and depressive episode with insufficient symptoms (American Psychiatric Association 2013).

1.1.2 Bipolar and Related Disorders

In bipolar I disorder, a manic episode can be preceded or followed by a hypomanic episode or a major depressive episode. The manic episode is characterized by a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting, at least, 1 week (or any duration if hospitalization is necessary). During this period, three or more of the following symptoms are present (four if the mood is only irritable):

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (e.g., feels rested after only 3 h of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (nondirected activity)
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

The hypomanic episode is characterized by the same symptoms, but differs in severity and duration (at least 4 days) (American Psychiatric Association 2013).

Bipolar II disorder is characterized by one or more major depressive episodes, accompanied by at least one hypomanic episode, the symptoms of both being those described above (American Psychiatric Association 2013).

A cyclothymic disorder is characterized by at least 2 years of numerous periods of hypomanic and depressive symptoms that do not meet criteria for a manic episode and for a major depressive episode, respectively (American Psychiatric Association 2013).

In substance/medication-induced bipolar and related disorder, a prominent and persistent disturbance of mood or loss of interest or pleasure as a direct physiological consequence of a drug of abuse, a medication, another somatic treatment for depression, or toxin exposure is observed (American Psychiatric Association 2013).

Bipolar and related disorder due to another medical condition consists of a prominent and persistent disturbance of mood and increased energy and activity as a direct physiological consequence of another medical condition (American Psychiatric Association 2013).

Other specified bipolar and related disorder and unspecified bipolar and related disorder are disorders with bipolar features that do not meet criteria for any of the specified bipolar disorders. In the first group, the clinician chooses to communicate the specific reason why the presentation does not meet criteria for any specified bipolar and related disorder, while in the second one, he does not specify. Other specified bipolar and related disorders include the following presentations: (1) short-duration hypomanic (2–3 days) and major depressive episodes, (2) hypomanic episodes with insufficient symptoms and major depressive episodes, (3) hypomanic episode without prior major depressive episode, and (4) short-duration cyclothymia (less than 24 months).

1.2 Prevalence

According to the World Health Organization (WHO), more than 350 million people of all ages suffer from depression (WHO 2015). Unfortunately, the condition of 10–40 % of them does not improve with the current drug therapies or shows a partial response combined with functional impairment, poor quality of life, suicide ideation and attempts, self-injurious behavior, and high relapse rate (Møldrup and Oestergaard 2011; Al-Harbi 2012).

Mental health conditions are a leading cause of disability-adjusted life years (DALYs) worldwide, neuropsychiatric disorders accounting to 199 million DALYs (Bloom et al. 2011). In particular, unipolar depressive disorders correspond to 65 million DALYs and bipolar affective disorder to 14 million DALYs (WHO 2008).

Among the top 25 causes of global years lived with disability (YLDs) in 2013, major depression and dysthymia are the 2nd and the 16th leading causes, respectively, while in 1990 were ranked in lower positions (3rd and the 20th positions, respectively). Bipolar disorder occupies the 17th position (19th in 1990) (Global Burden of Disease Study 2013 Collaborators 2015). Alarming, the report from WHO published in 2008 foresees that unipolar depressive disorders will be the first cause of DALYs by the year 2030 (WHO 2008).

The Global Burden of Disease (GBD) Study 2013 ranked the prevalence and YLDs of several diseases and the results for depressive disorders (comprising major depressive disorder and persistent depressive disorder) and bipolar disorder (BPD) are shown in Tables 1.1 and 1.2.

Table 1.1 Prevalence and YLDs 2013 (thousands) by age for depressive disorders and bipolar disorder (Global Burden of Disease Study 2013 Collaborators 2015)

Age	Depressive disorders		Bipolar disorder	
	Prevalent cases (thousands)	YLDs (thousands)	Prevalent cases (thousands)	YLDs (thousands)
0–6 days	–	–	–	–
7–27 days	–	–	–	–
28–364 days	–	–	–	–
1–4 years	320.0	68.7	–	–
5–9 years	5544.8	1169.4	–	–
10–14 years	13709.7	2773.5	641.8	136.0
15–19 years	24403.6	4709.3	2958.1	623.8
20–24 years	33395.4	6187.4	5891.0	1232.1
25–29 years	35658.5	6391.7	7037.7	1460.9
30–34 years	34041.5	5972.3	6261.2	1290.2
35–39 years	32901.7	5662.0	5392.9	1102.7
40–44 years	32586.6	5516.2	4716.7	957.8
45–49 years	30754.8	5143.9	4044.6	814.8
50–54 years	27309.0	4525.2	3333.6	665.1
55–59 years	23511.0	3849.7	2667.3	525.8
60–64 years	20370.4	3296.4	2141.7	416.5
65–69 years	13771.9	2196.6	1352.3	258.9
70–74 years	11222.5	1762.4	1032.9	194.4
75–79 years	7963.2	1221.9	691.1	127.3
+80 years	8135.7	1186.1	598.6	104.9

Table 1.2 Global prevalence and YLDs 2013 (thousands) of depressive disorders and bipolar disorder (Global Burden of Disease Study 2013 Collaborators 2015)

Country	Prevalent cases 2013 (thousands)		YLDs 2013 (thousands)	
	Depressive disorders	Bipolar disorder	Depressive disorders	Bipolar disorder
Afghanistan	976.6	168.3	172.3	34.0
Albania	152.0	22.9	26.0	4.6
Algeria	2097.2	310.1	381.1	63.2
Andorra	4.3	0.6	0.7	0.1
Angola	1041.7	111.7	193.1	22.7
Antigua and Barbuda	5.0	0.7	0.9	0.1
Argentina	1992.7	331.3	336.0	67.6
Armenia	158.6	22.5	27.4	4.6
Australia	1573.6	213.7	272.3	43.0
Austria	444.0	65.5	73.7	13.2
Azerbaijan	488.7	71.0	85.0	14.5
Bahrain	78.1	11.9	14.3	2.4
Bangladesh	8126.1	1097.9	1434.8	221.6
Barbados	16.8	2.4	2.9	0.5
Belarus	628.9	76.7	108.8	15.5
Belgium	500.6	82.7	79.8	16.6
Belize	15.9	2.4	2.9	0.5
Benin	531.9	58.7	97.6	11.9
Bhutan	38.2	5.4	6.8	1.1
Bolivia	503.0	74.2	90.5	15.2
Bosnia and Herzegovina	198.1	29.8	33.4	6.0
Botswana	112.5	13.6	20.5	2.8
Brazil	11154.4	1597.9	1961.1	323.9
Brunei	18.3	2.7	3.1	0.6
Bulgaria	388.0	54.0	64.3	10.8
Burkina Faso	788.9	91.3	145.9	18.7
Burundi	580.6	56.2	109.7	11.5
Cambodia	483.7	91.7	77.9	18.6
Cameroon	1011.1	124.7	184.2	25.3
Canada	1741.3	284.5	279.7	57.5
Cape Verde	30.6	3.4	5.6	0.7
Central African Republic	243.6	27.5	44.4	5.5
Chad	530.6	65.0	96.6	13.2
Chile	889.2	146.2	150.2	29.8
China	63932.0	8321.3	10691.0	1706.7
Colombia	3404.0	469.4	628.5	95.1
Comoros	45.7	4.3	8.6	0.9
Congo	234.4	25.5	43.1	5.2

(continued)

Table 1.2 (continued)

Country	Prevalent cases 2013 (thousands)		YLDs 2013 (thousands)	
	Depressive disorders	Bipolar disorder	Depressive disorders	Bipolar disorder
Costa Rica	307.7	43.9	56.2	8.9
Cote d'Ivoire	950.0	116.5	172.1	23.6
Croatia	225.4	33.8	37.6	6.8
Cuba	689.1	99.1	119.4	19.9
Cyprus	47.4	7.0	8.0	1.4
Czech Republic	556.6	85.5	92.2	17.0
Democratic Republic of the Congo	3387.8	367.2	619.6	73.7
Denmark	286.5	41.2	47.9	8.3
Djibouti	59.4	5.8	11.1	1.2
Dominica	3.9	0.6	0.7	0.1
Dominican Republic	529.6	78.2	95.0	16.0
Ecuador	791.9	116.7	141.7	23.9
Egypt	2701.1	603.5	447.9	122.3
El Salvador	323.9	50.4	58.0	10.2
Equatorial Guinea	41.2	4.5	7.6	0.9
Eritrea	377.4	36.7	70.6	7.4
Estonia	122.2	10.7	22.0	2.1
Ethiopia	5200.0	528.2	966.0	107.8
Federated States of Micronesia	3.0	0.5	0.5	0.1
Fiji	30.0	5.0	4.9	1.0
Finland	344.9	43.8	58.7	8.7
France	3608.4	465.9	611.9	93.7
Gabon	92.5	10.2	16.8	2.0
Georgia	244.8	33.5	41.8	6.8
Germany	4001.4	605.5	640.1	120.6
Ghana	1398.5	158.4	257.9	32.4
Greece	566.7	84.4	93.7	17.0
Grenada	5.6	0.8	1.0	0.2
Guatemala	638.5	104.7	114.1	21.2
Guinea	558.2	66.1	102.4	13.5
Guinea-Bissau	72.9	9.8	13.1	2.0
Guyana	36.9	5.5	6.6	1.1
Haiti	477.9	71.4	85.4	14.5
Honduras	499.8	60.4	93.6	12.3
Hungary	534.1	80.2	89.5	16.1
Iceland	13.4	2.2	2.2	0.5
India	65346.3	8730.7	11529.6	1774.8

(continued)

Table 1.2 (continued)

Country	Prevalent cases 2013 (thousands)		YLDs 2013 (thousands)	
	Depressive disorders	Bipolar disorder	Depressive disorders	Bipolar disorder
Indonesia	8569.5	1592.4	1407.7	327.9
Iran	4526.3	654.6	823.7	133.3
Iraq	1175.2	213.8	207.2	43.5
Ireland	262.6	33.5	45.0	6.8
Israel	352.0	49.7	59.5	10.1
Italy	3285.0	474.1	537.3	94.7
Jamaica	148.6	21.5	26.4	4.4
Japan	6087.4	854.7	985.3	173.6
Jordan	377.1	53.0	69.1	10.8
Kazakhstan	824.1	118.4	142.5	24.1
Kenya	2710.2	258.6	510.3	52.7
Kiribati	3.2	0.6	0.5	0.1
Kuwait	191.7	28.4	35.3	5.8
Kyrgyzstan	257.4	37.2	45.4	7.6
Laos	194.6	38.1	31.9	7.8
Latvia	97.4	15.9	15.6	3.2
Lebanon	242.0	40.5	42.3	8.2
Lesotho	123.5	13.0	22.6	2.6
Liberia	181.2	24.3	32.1	4.9
Libya	334.0	48.0	60.6	9.7
Lithuania	197.9	22.7	34.1	4.6
Luxembourg	27.5	4.1	4.6	0.8
Macedonia	106.6	16.5	18.0	3.3
Madagascar	1405.5	130.5	262.9	26.4
Malawi	910.8	88.0	170.5	17.9
Malaysia	1070.0	197.4	176.7	40.6
Maldives	11.5	2.2	1.9	0.5
Mali	639.5	78.9	117.0	16.1
Malta	22.7	3.3	3.8	0.7
Marshall Islands	2.1	0.3	0.3	0.1
Mauritania	205.5	23.0	37.8	4.7
Mauritius	50.7	8.9	8.3	1.8
Mexico	6900.0	1023.3	1259.2	209.5
Moldova	224.7	27.8	39.2	5.6
Mongolia	135.3	20.2	23.8	4.2
Montenegro	30.9	4.7	5.2	0.9
Morocco	1721.3	256.3	309.6	52.0
Mozambique	1433.5	138.9	265.2	27.9
Myanmar	1917.0	358.3	312.2	73.4

(continued)

Table 1.2 (continued)

Country	Prevalent cases 2013 (thousands)		YLDs 2013 (thousands)	
	Depressive disorders	Bipolar disorder	Depressive disorders	Bipolar disorder
Namibia	126.3	14.7	23.0	3.0
Nepal	977.7	178.4	163.3	36.4
Netherlands	769.6	134.0	123.2	26.8
New Zealand	240.7	47.0	40.1	9.5
Nicaragua	332.6	48.1	60.7	9.7
Niger	781.1	86.8	144.7	17.8
Nigeria	7706.8	957.2	1378.7	191.8
North Korea	1014.2	139.7	165.7	28.5
Norway	244.0	37.8	40.3	7.6
Oman	188.7	30.8	34.7	6.3
Pakistan	9356.6	1175.9	1679.5	239.8
Palestine	313.3	27.3	60.3	5.6
Panama	220.7	32.4	40.1	6.6
Papua Nova Guinea	209.6	36.2	34.8	7.4
Paraguay	323.8	48.2	57.9	9.8
Peru	1580.3	232.8	281.5	47.2
Philippines	3046.9	575.2	501.0	117.8
Poland	2031.6	312.3	340.6	62.8
Portugal	705.8	82.2	120.5	16.4
Qatar	130.3	21.1	24.0	4.3
Romania	1139.4	189.3	190.9	38.2
Russia	9400.4	1169.3	1619.0	235.8
Rwanda	736.6	67.7	137.4	13.6
Saint Lucia	10.2	1.5	1.8	0.3
Saint Vincent and the Grenadines	5.9	0.9	1.0	0.2
Samoa	5.6	0.9	0.9	0.2
Sao Tome and Principe	10.3	1.1	1.9	0.2
Saudi Arabia	1553.6	224.4	282.7	45.3
Senegal	728.5	80.0	134.4	16.3
Serbia	489.9	74.8	82.8	15.1
Seychelles	3.6	0.6	0.6	0.1
Sierra Leone	289.4	35.4	52.8	7.2
Singapore	276.3	27.5	49.2	5.6
Slovakia	287.0	44.6	48.3	9.0
Slovenia	109.5	16.7	18.2	3.3
Solomon Islands	15.6	2.7	2.6	0.6
Somalia	576.6	54.1	108.6	11.0
South Africa	2728.7	376.5	475.5	75.3

(continued)

Table 1.2 (continued)

Country	Prevalent cases 2013 (thousands)		YLDs 2013 (thousands)	
	Depressive disorders	Bipolar disorder	Depressive disorders	Bipolar disorder
South Korea	1926.2	344.4	296.9	70.0
South Sudan	627.8	64.4	115.0	12.9
Spain	2641.5	366.5	441.1	73.6
Sri Lanka	810.6	142.9	131.8	29.2
Sudan	1712.9	233.6	311.9	47.3
Suriname	28.3	4.2	5.0	0.9
Swaziland	60.6	7.7	10.9	1.5
Sweden	551.4	71.8	93.2	14.4
Switzerland	405.4	62.1	65.8	12.4
Syria	1106.0	152.6	202.7	31.0
Taiwan	722.6	146.7	102.1	29.9
Tajikistan	347.7	50.3	61.6	10.3
Tanzania	2858.5	269.7	536.7	54.8
Thailand	2816.9	489.3	455.8	100.3
The Bahamas	21.5	3.2	3.8	0.6
The Gambia	114.9	10.0	21.9	2.0
Timor-Leste	24.7	5.1	4.0	1.0
Togo	343.4	39.6	63.3	8.1
Tonga	3.2	0.5	0.5	0.1
Trinidad and Tobago	76.8	11.5	13.5	2.3
Tunisia	648.6	91.5	117.7	18.6
Turkey	3323.1	600.6	573.7	121.7
Turkmenistan	247.7	36.3	43.6	7.5
Uganda	2272.8	189.6	432.1	38.5
Ukraine	3065.7	375.7	523.3	75.7
United Arab Emirates	528.9	91.5	97.9	18.9
United Kingdom	3019.6	475.1	492.8	95.5
United States	19695.5	2471.8	3340.3	496.4
Uruguay	168.5	27.4	28.2	5.6
Uzbekistan	1365.7	198.5	240.9	40.8
Vanuatu	7.4	1.3	1.2	0.3
Venezuela	1684.7	252.1	305.9	51.4
Vietnam	3795.6	635.7	629.2	129.7
Yemen	857.2	151.5	152.1	30.9
Zambia	790.5	76.8	147.5	15.5
Zimbabwe	681.5	84.8	123.7	17.1

1.3 Economic Burden

Based on the data published by Hu (2006), plus new reports from the United States, China, Kenya, and Australia, the World Economic Forum, and the Harvard School of Public Health estimated that the global cost of mental health conditions in 2010 was US\$2.5 trillion (US\$1.6 and 0.9 trillion from high-income and low-income countries, respectively), with the costs projected to rise to US\$6.0 trillion by 2030. Two-thirds of the total costs correspond to indirect costs (i.e., lost income due to mortality, disability, care seeking, or other and nonpersonal costs), and the remaining are from direct costs (i.e., personal medical care costs and personal nonmedical care costs) (Bloom et al. 2011).

Concerning only depressive disorders, the economic burden of depression, including MDD, BPD, and persistent depressive disorder, was estimated at US\$83.1 billion in 2000 in the United States. This total comprised US\$26.1 billion from direct medical costs, US\$5.4 billion from suicide-related mortality costs, and US\$51.5 billion from indirect workplace costs. The economic burden of MDD, in particular, was US\$173.2 billion in 2005 and US\$210.5 billion in 2010, direct costs accounting to US\$77.5 billion in 2005 and US\$98.9 billion in 2010 (Greenberg et al. 2015).

The scenario in Europe is also alarming. In a study comprising data from Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and United Kingdom, the cost of brain disorders in 2010 was €798 billion, direct health care costing 37 %, direct nonmedical cost corresponding to 23 %, and indirect cost to 40 %. MDD and BPD caused direct costs of 37.9 and 3.5 billion euros and indirect costs of 54.0 and 18.0 billion euros, respectively (Olesen et al. 2012).

The total estimated cost of depression in China was US\$6.2 billion in 2002. Direct and indirect costs were about 16 and 84 % of the total cost of depression, respectively (Hu et al. 2007).

In Australia, depression costs approximately US\$12.6 billion per year (Manicavasagar 2012). Indirect cost per patient was around US\$134.3 thousand for bipolar disorder I, US\$76.8 thousand for bipolar disorder II, and US\$68.3 thousand for unipolar depression. Direct costs for the same disorders were around US\$26.3 thousand, US\$17.6 thousand, and US\$27.2 thousand per patient, respectively (Parker et al. 2013).

In 2001, South Africa spent US\$88 per patient with BPD with medical management, while with medication the costs were almost ten times higher (US\$751 per patient) (McLeod et al. 2002). On the other hand, in a study performed between 2002 and 2004, severe depression in South Africa was associated with indirect costs of US\$4798 per patient/year (Lund et al. 2013).