Journal of Affective Disorders 169 S1 (2014) S3–S11

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

The prevalence and burden of bipolar depression

Shefali Miller[a,b,*], Bernardo Dell'Osso[a,c], Terence A. Ketter[a]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA
[b] Sierra Pacific Mental Illness Research Education and Clinical Centers, Palo Alto VA Health Care System, Palo Alto, CA, USA
[c] Department of Psychiatry, University of Milan; Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122, Milan, Italy

ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form 8 August 2014
Accepted 3 September 2014

Keywords:
Bipolar disorder
Depression
Prevalence
Burden
Cost
Functioning

ABSTRACT

Background: Bipolar disorder is characterized by debilitating episodes of depression and mood elevation (mania or hypomania). For most patients, depressive symptoms are more pervasive than mood elevation or mixed symptoms, and thus have been reported in individual studies to impose a greater burden on affected individuals, caregivers, and society. This article reviews and compiles the literature on the prevalence and burden of syndromal as well as subsyndromal presentations of depression in bipolar disorder patients.
Methods: The PubMed database was searched for English-language articles using the search terms "bipolar disorder," "bipolar depression," "burden," "caregiver burden," "cost," "costs," "economic," "epidemiology," "prevalence," "quality of life," and "suicide." Search results were manually reviewed, and relevant studies were selected for inclusion as appropriate. Additional references were obtained manually from reviewing the reference lists of selected articles found by computerized search.
Results: In aggregate, the findings support the predominance of depressive symptoms compared with mood elevation/mixed symptoms in the course of bipolar illness, and thus an overall greater burden in terms of economic costs, functioning, caregiver burden, and suicide.
Limitations: This review, although comprehensive, provides a study-wise aggregate (rather than a patient-wise meta-analytic) summary of the relevant literature on this topic.
Conclusions: In light of its pervasiveness and prevalence, more effective and aggressive treatments for bipolar depression are warranted to mitigate its profound impact upon individuals and society. Such studies could benefit by including metrics not only for mood outcomes, but also for illness burden.

Contents

1. Introduction S4
2. Methods S4
3. Prevalence and epidemiology of bipolar disorder S4
4. Predominance of depression in bipolar illness course S5
5. Socioeconomic burden of bipolar disorder S5
6. Impact of bipolar depression on the socioeconomic burden of bipolar disorder S6
7. Impact of bipolar depression on individual functioning and quality of life S7
8. Caregiver burden of bipolar depression S8
9. Suicide, suicide attempts, and burden of bipolar depression S8
10. Polypharmacy in bipolar depression S8
11. Management of burden associated with bipolar depression S8
12. Limitations of the study S9
13. Conclusions S9
Disclosures S9
Conflict of interest S9
Funding/support S9
Contributor's statement S9
Acknowledgments S9
References S9

* Corresponding author at: 401 Quarry Road, Stanford, CA 94305-5723, USA.
Tel.: +1 650 725 8203; fax: +1 650 724 9900.
E-mail address: shefalis@stanford.edu (S. Miller).

0165-0327/

1. Introduction

Bipolar disorder (BD) is a serious, commonly disabling psychiatric condition that is tragically, on occasion, fatal. It is characterized by recurrent episodes of depression and mood elevation (mania or hypomania). Bipolar spectrum illness (comprising BD in its broadest sense), including bipolar I disorder (BDI, requiring a lifetime history of at least one manic episode), bipolar II disorder (BDII, requiring a lifetime history of major depressive and hypomanic episodes, without any history of mania), and BD not otherwise specified (BDNOS, including subthreshold bipolar presentations), may affect as much as 4.4% of the US population (Merikangas et al., 2007). Despite its lower prevalence compared with some other mental disorders, such as unipolar major depressive disorder (MDD, which has an approximately 3-fold higher lifetime prevalence) and anxiety disorders (which in aggregate have an approximately 6-fold higher lifetime prevalence) (Kessler et al., 2005), BD causes more marked functional impairment (Shippee et al., 2011; Solé et al., 2012) and greater reduction in quality of life (QOL) (Gutierrez-Rojas et al., 2008; Sierra et al., 2005). As a result, BD imposes a greater economic burden to society (i.e., higher costs) than other mental disorders (Kleinman et al., 2005; Peele et al., 2003) and constitutes the 12th leading cause of disability worldwide across all age groups (World Health Organization, 2008).

The course of bipolar illness is characterized by the predominance of depressive symptoms, which are more pervasive than mood elevation or mixed symptoms. Prospective studies consistently show that BD patients spend more time with depressive symptoms than with mood elevation/mixed symptoms (Judd et al., 2003; Judd et al., 2002; Kupka et al., 2007). Consequently, depressive symptoms compared with mood elevation/mixed symptoms have been consistently associated with greater (or at least equal) impairments of social and occupational functioning (Bonnin et al., 2010; Calabrese et al., 2004; Gitlin et al., 2011) and QOL (Gutierrez-Rojas et al., 2008; Revicki et al., 2005; Zhang et al., 2006). The present article aims to review the prevalence of bipolar depression and discuss the impact of depressive symptoms on the overall burden of BD.

2. Methods

The PubMed database was searched in February 2013 for English-language articles using the following search terms: "bipolar disorder," "bipolar depression," "burden," "caregiver burden," "cost," "costs," "economic," "epidemiology," "prevalence," "quality of life," and "suicide." The search results were reviewed, and studies related to the epidemiology and burden of BD and bipolar depression were manually selected for inclusion as appropriate. Additional references were obtained manually by reviewing the reference lists of relevant articles found by computerized search.

3. Prevalence and epidemiology of bipolar disorder

BD affected an estimated 29.5 million individuals worldwide in 2004, according to the World Health Organization (World Health Organization, 2008). A more recent (2011) study involving a combined sample of 61,392 community-dwelling individuals in 11 countries, mainly in the Americas, Europe, and Asia, found an aggregate lifetime BD prevalence of 2.4% (0.6% BDI, 0.4% BDII, and 1.4% subthreshold BD) (Merikangas et al., 2011). Of the 11 countries examined in this study, the United States had the highest lifetime prevalence of bipolar spectrum illness (combined BDI, BDII, and subthreshold BD) at 4.4%, while India had the lowest prevalence of bipolar spectrum illness at 0.1% (Merikangas et al., 2011).

In the United States, the estimated 12-month prevalence rates of BDI, BDII, and subthreshold BD were 0.6%, 0.8%, and 1.4%, respectively (Merikangas et al., 2007). BD prevalence decreased with increasing age and education level and was higher in unemployed/disabled individuals compared with employed individuals, but did not appear to be consistently related to gender, race/ethnicity, or income (Merikangas et al., 2007). Typical age at onset of BD was late adolescence to young adulthood (Merikangas et al., 2007). Childhood-onset BD occurs with prevalence estimates of 0.1% to 2.5% in pediatric samples, and there is some potentially substantive geographic variation (Merikangas et al., 2012; Stringaris et al., 2010). For example, childhood-onset BD may be more common in the United States than in Europe (Post et al., 2008). Indeed, among the first 1000 participants in the US-based Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), 27.7% had childhood onset (age <13 years), which was associated with greater number of lifetime depressive and manic episodes, and greater likelihood of past suicide attempt, compared with adolescent onset (age 13–18 years) and adult onset (age >18 years) (Perlis et al., 2004). Thus, childhood-onset BD, which may entail greater genetic vulnerability (offspring of parents with BD may be at particular risk for this form of BD) (Goodwin and Jamison, 2007), could represent one of the more costly forms of BD.

BD has been consistently associated with significant medical and psychiatric comorbidity. For example, in the National Comorbidity Survey Replication (NCS-R), 94.6% of patients with BD reported having at least one comorbid disorder, with a mean of 4.6 medical and/or psychiatric comorbidities reported by such individuals (Gadermann et al., 2012). Moreover, in a Stanley Foundation Bipolar Treatment Outcome Network (SFBN) study, among 288 BD patients assessed by structured diagnostic interview, 65% had at least one comorbid Axis I disorder, with anxiety and substance use disorders being the predominant comorbidities (McElroy et al., 2001). In STEP-BD, 58.8% of BD patients had at least one medical comorbidity, and the prevalence was significantly higher in those with lifetime anxiety and substance use disorders (Magalhaes et al., 2012). In addition, analysis of the National Hospital Discharge Survey showed that among patients discharged with a primary diagnosis of BD, 74.6% had at least one comorbid condition, and patients with a primary diagnosis of BD had a greater burden of most psychiatric and some general medical comorbidities, compared with those without a BD diagnosis (Weber et al., 2011).

With regard to medical comorbidities, cardiovascular and metabolic diseases are particularly prevalent among BD patients, who have shown elevated rates of hypertension, obesity, metabolic syndrome, and diabetes (Fiedorowicz et al., 2008; Goldstein et al., 2011; McIntyre et al., 2005; Vancampfort et al., 2013). A large population-based cohort study in Sweden found that patients with BD had increased mortality rates due to cardiovascular and other medical illnesses, dying of cardiovascular disease, on average, 10 years earlier than the general population (Westman et al., 2013); these results are consistent with findings from a recent review of the literature (Roshanaei-Moghaddam and Katon, 2009). Medical illness burden may have important implications for BD mood outcomes. For example, in post hoc analyses of two clinical trials involving 225 rapid-cycling BDI and BDII participants, endocrine/metabolic illness burden was inversely correlated with remission from depression, and higher body mass index was associated with lower likelihood of response or remission (Kemp et al., 2010). Moreover, results from a Canadian population-based study associated chronic medical conditions with more severe bipolar illness course, poorer functioning, and increased medical service utilization among BD patients (McIntyre et al., 2006).

As noted above, psychiatric comorbidities are also particularly prevalent in BD patients; more than 90% of BDI and BDII patients

in the NCS-R reported at least one comorbid psychiatric condition (Merikangas et al., 2007). Anxiety, impulse control, and substance use disorders were two to three times more prevalent among BD patients than in the general population (Kessler et al., 2005; Merikangas et al., 2007). Anxiety disorder comorbidity was associated with multiple unfavorable BD illness characteristics, including earlier age at first depressive episode and greater number of depressive episodes, in a sample of 1416 BD patients, and was associated with fewer days well, longer time to recovery from depression, shorter time to mood episode relapse, and poorer role functioning and QOL, during 12-month prospective follow-up of the first 1000 STEP-BD patients (Goes et al., 2012; Otto et al., 2006). Similarly, current or past substance use disorder was associated with poorer role functioning, lower self-reported QOL, and greater likelihood of past suicide attempt among the first 1000 STEP-BD participants (Weiss et al., 2005). Among 288 patients evaluated within the SFBN, current Axis I comorbidity was associated with earlier age at BD onset, history of cycle acceleration, and development of more severe mood episodes over time (McElroy et al., 2001). Patterns of Axis I comorbidity among BD patients may be influenced by age. One study demonstrated that younger (≤30 years old) BD patients had more comorbidities and were more likely to have substance use disorder and anorexia compared with older (>30 years old) BD patients, although the latter group more frequently had obsessive compulsive disorder (Dell'osso et al., 2011).

4. Predominance of depression in bipolar illness course

Individuals with BD have consistently been shown to spend a greater proportion of time with depressive symptoms than with mood elevation/mixed symptoms. Among US-based participants in the National Institute of Mental Health (NIMH) Collaborative Depression Study, 146 BDI and 86 BDII patients were followed prospectively with weekly symptom status ratings, assessed by interviews by trained raters every 6 months for the first 5 years, then yearly, for a mean of 12.8 and 13.4 years, respectively (Judd et al., 2003; Judd et al., 2002). On average, BDI patients spent 31.9% of weeks with depressive symptoms (22.9% subsyndromal and 8.9% syndromal), compared with 9.3% of weeks with mood elevation (2.4% subsyndromal, 4.6% syndromal hypomanic, and 2.3% syndromal manic), 5.9% of weeks with cycling/mixed symptoms, and 52.7% of weeks with euthymia (Judd et al., 2002). BDII patients, compared with BDI patients, spent a numerically greater proportion of time depressed: 50.3% of total weeks with depressive symptoms (37.4% subsyndromal and 12.9% syndromal), 1.3% of weeks with hypomania (0.4% subsyndromal and 0.9% syndromal), 2.3% of weeks with cycling/mixed symptoms, and 46.1% of weeks with euthymia (Judd et al., 2003).

As depicted in Figure 1, other prospective studies have consistently yielded similar results despite variable geography and methodology, showing that BD patients have more frequent depressive symptoms than mood elevation/mixed symptoms (in aggregate, 34.1% of the time depressed versus 12.3% of the time elevated/mixed) (De Dios et al., 2010; Joffe et al., 2004; Judd et al., 2003; Judd et al., 2002; Kupka et al., 2007). For example, among 405 US and European SFBN patients with BDI evaluated for 1 year with prospective daily self-ratings using the NIMH Life Chart Methodology, results showed subsyndromal/syndromal depression 36.0% of the time, hypomania 11.5%, mania 1.0%, cycling 3.7%, and euthymia 47.7% of the time (Kupka et al., 2007). In this same study, 102 BDII patients had subsyndromal/syndromal depression 36.9% of the time, hypomania 9.8%, subsyndromal hypomania 0.2%, cycling 2.8%, and euthymia 50.2% of the time (Kupka et al., 2007). In a different Canadian study of 138 BDI and BDII patients followed prospectively for at least one year (mean

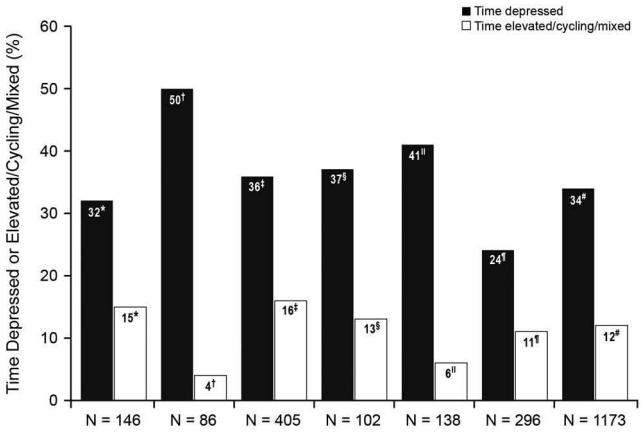

Fig. 1. Percentage of time spent depressed or elevated/cycling/mixed in bipolar disorder (BD): summary of findings from prospective studies (De Dios et al., 2010; Joffe et al., 2004; Judd et al., 2003; Judd et al., 2002; Kupka et al., 2007). Data from * Judd et al. 2002 (bipolar I disorder [BDI]); † Judd et al. 2003 (bipolar II disorder [BDII]); ‡ Kupka et al. 2007 (BDI); § Kupka et al. 2007 (BDII); || Joffe et al. 2004 (BDI/II); and ¶ De Dios et al. 2010 (BD spectrum); # Pooled average across studies, weighted based on sample size.

1227 days) with mood ratings recorded by clinicians at each visit using a modified version of the NIMH Life Chart Methodology, 40.9% of the time was spent with subsyndromal/syndromal depression, compared with 6% with subsyndromal/syndromal mood elevation (Joffe et al., 2004). In a prospective 18-month follow-up of a Spanish cohort of 296 BD spectrum patients (BDI, BDII, BDNOS, cyclothymia, and schizoaffective disorder-bipolar type), quarterly assessments were made, including estimation of days spent in mood episodes and days spent euthymic since the last visit (De Dios et al., 2010). This study yielded broadly consistent results regarding the primacy of depressive compared with mood elevation symptoms; patients spent 23.7% of days depressed, 8.3% of days elevated, 2.6% of days mixed, and 65.5% of days euthymic (De Dios et al., 2010).

Effects of gender and age on the prevalence of bipolar depression have also been studied. In an SFBN study involving 406 female and 305 male BDI and BDII patients followed for up to 7 years, the predominance of depressive symptoms appeared more pronounced in women (Altshuler et al., 2010). Thus, women were depressed for 35.6% of the time compared with 28.7% for men, whereas men spent a greater proportion of time euthymic (56.9% for men versus 50.4% for women) (Altshuler et al., 2010). In contrast, men and women had similar percentages of time elevated (14.1% for women versus 14.4% for men) (Altshuler et al., 2010). In a separate study involving 164 STEP-BD patients seen on average once per month, 47 women of menopausal transition age (45–55 years) and 30 similar-aged men, plus 48 women and 39 men aged 30–40 years, were monitored naturalistically for a mean of 30 months (Marsh et al., 2009). Among these patients, women at the menopausal transition age spent a greater proportion of visits with depressive symptoms and a lower proportion of visits euthymic compared with the pooled comparison group of men and younger premenopausal women (Marsh et al., 2009).

5. Socioeconomic burden of bipolar disorder

BD imposes substantial economic and psychosocial burdens on individuals as well as society. Regarding economic burden in the United States, indirect costs (e.g., lost productivity of patients and caregivers) may be approximately 4-fold higher than direct costs (e.g., treatment-related costs of inpatient and outpatient care, and treatment-unrelated costs of services used by BD patients, such as

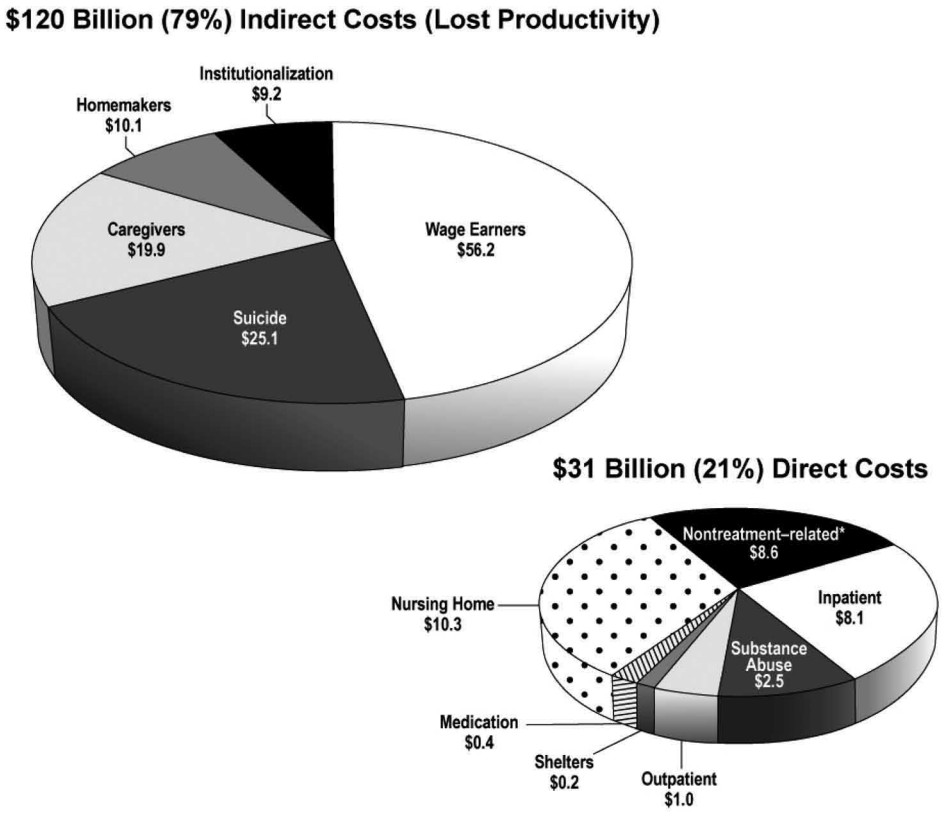

Fig. 2. Estimated indirect and direct costs of bipolar disorder in the United States in 2009 (in billions) (Dilsaver, 2011; Wyatt and Henter, 1995). *Criminal justice system use, suicide, or suicide attempt. Data from Dilsaver, S.C., 2011, J Affect. Disord. 129 (1-3), 79–83; Wyatt, R.J., Henter, I., 1995, Soc. Psychiatry Psychiatr Epidemiol. 30 (5), 213–219.

the criminal justice system). Thus, in 2009, the estimated total cost of BDI and BDII in the United States was $151 billion, consisting of $30.7 billion in direct and $120.3 billion in indirect costs (Figure 2) (Dilsaver, 2011; Wyatt and Henter, 1995). These data were derived from a 1991 estimate, adjusted for the increased prevalence of bipolar disorders in 2009, inflation, and population growth, and demonstrate the primacy of indirect compared with direct costs (Dilsaver, 2011; Wyatt and Henter, 1995). Analysis of employer-sponsored health insurance claims for 1.7 million individuals in 1996 showed that BD was the most expensive behavioral health diagnosis, resulting in higher annual health care costs for both individual patients and insurance plans (Peele et al., 2003). A more recent analysis of employer-based health plan data for 80,000 enrollees from 2004 to 2007 found the monthly per-patient costs of BD to be greater than those of all other psychiatric or medical diagnoses, with the exception of diabetes concomitant with coronary artery disease (Williams et al., 2011). In these and other analyses of health plan data, inpatient treatment (psychiatric and/or non-psychiatric) accounted for the greatest proportion of direct health care costs associated with BD, outweighing the costs of medications and outpatient visits (Bryant-Comstock et al., 2002; Guo et al., 2008; Guo et al., 2007; Peele et al., 2003; Williams et al., 2011).

In addition to the direct economic costs of health care, BD appears to be associated with even greater indirect costs due to unemployment and lost workplace productivity. In a study of 219 patients with BDI compared with 198 patients without serious mental illness, recruited from physician practices across the United States, BDI patients were significantly more likely to have been fired or laid off, or to have received short- or long-term disability for a medical reason (McMorris et al., 2010). Similarly, patients with BD (or subthreshold presentations of BD) in the NIMH Epidemiological Catchment Area Program database were approximately twice as likely as individuals without a mental disorder to have relied upon welfare or disability benefits (Judd and Akiskal, 2003). In addition, BD patients have high rates of absenteeism, even in comparison with unipolar MDD patients, which imposes a significant economic burden on employers (Gardner et al., 2006; Kessler et al., 2006; McMorris et al., 2010; Shippee et al., 2011; Zimmerman et al., 2010). In an NCS-R–derived nationally representative sample of 3378 US workers, BD was associated with 65.5 lost workdays per worker per year, yielding a projected annual salary-equivalent cost of lost productivity in the United States of $14 billion (Kessler et al., 2006). It is important to note that this study included assessment of absenteeism (missed days of work) as well as presenteeism (low performance while at work) in the estimation of lost workdays (Kessler et al., 2006). BD results in lost productivity not only for patients, but also for their family members, whose workforce participation is compromised by caregiver responsibilities. In 1991, lost family member occupational productivity was estimated to account for 16.5% of the indirect costs, or 13.8% of the total costs, of BD in the United States (Wyatt and Henter, 1995).

6. Impact of bipolar depression on the socioeconomic burden of bipolar disorder

Depressive symptoms contribute substantially to the socioeconomic burden of BD and may account for a greater proportion of the overall costs of BD compared with manic or mixed symptomatology. This could be due to much higher indirect costs for depression (which is far more pervasive over time than mood elevation) due to lost productivity, even though the direct costs of manic/mixed symptoms exceed those of depression because of higher inpatient treatment expenses (Bryant-Comstock et al., 2002). In the nationally representative sample of 3378 US

workers from the NCS-R (described above), BD patients with at least one prior-year major depressive episode had greater levels of absenteeism, presenteeism, and total lost workdays compared with BD patients with only manic/hypomanic episode(s) during the previous 12 months (Kessler et al., 2006). In a sample of 412 BD outpatients (age <65 years) followed longitudinally over 24 months, unemployed compared with employed individuals had significantly greater severity of depressive but not manic/hypomanic symptoms (Simon et al., 2008). During monitoring, those having at least one major depressive episode were 15% less likely to be employed, and if employed, missed an additional 4 workdays per month, compared with those without significant depressive symptoms (Simon et al., 2008). In contrast, patients with at least one manic or hypomanic episode did not differ significantly from those without significant manic/hypomanic symptoms in terms of employment rates or number of missed workdays (Simon et al., 2008). Similarly, in a systematic review including nine prospective studies (*N*=3184), bipolar depression predicted worse employment status and/or occupational functioning more consistently than did mood elevation symptoms (Gilbert and Marwaha, 2012).

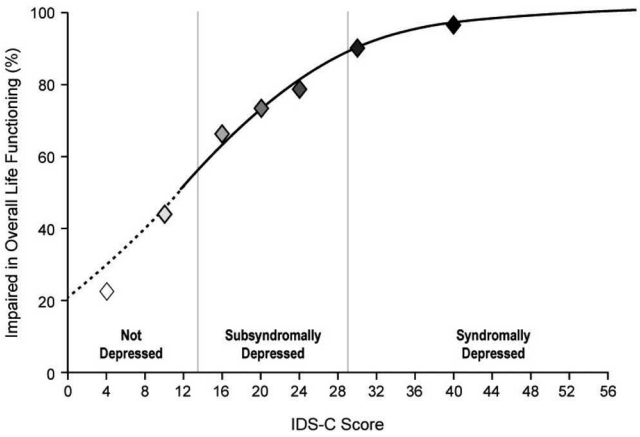

Fig. 3. Relationship between depressive symptoms and impaired life functioning. IDS-C = Inventory of Depressive Symptomatology – Clinician Rated (Altshuler et al., 2006). Altshuler et al., Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J Clin Psychiatry 67, 1551-1560, 2006. Copyright 2006, Physicians Postgraduate Press. Adapted by permission.

7. Impact of bipolar depression on individual functioning and quality of life

Beyond its impact on work functioning, bipolar depression is associated with substantial impairment of other domains of individual functioning, as well as reduced QOL. In a prospective follow-up study of 336 BDI and 105 BDII patients, depression symptom severity, independent of co-occurring manic/hypomanic symptoms, was consistently and strongly associated with functional impairment across multiple domains (work, social, household, and other activities) (Simon et al., 2007). On the other hand, manic/hypomanic symptom severity was less robustly associated with functional impairment in these domains, and the effect was further diminished after adjusting for co-occurring depressive symptoms (Simon et al., 2007). Similarly, among 158 BDI and 133 BDII patients followed prospectively for a mean of 15 years in the NIMH Collaborative Depression Study, depressive symptom severity correlated positively with psychosocial disability, to a similar or greater degree than manic/hypomanic symptom severity (Judd et al., 2005).

Cross-sectional and retrospective assessments have yielded similar findings as the prospective studies described above. Thus, in the NCS-R, 87.4% of BD patients reported severe role impairment due to a major depressive episode in the preceding 12 months, whereas only 56.6% reported such a level of role impairment due to a prior-year manic/hypomanic episode (Merikangas et al., 2007). In another study of 32 currently depressed patients compared with 31 currently manic/hypomanic BD patients, the depressed patients reported significantly greater impairments in autonomy, cognitive functioning, interpersonal relationships, leisure time, and overall functioning (Rosa et al., 2010). In yet another study of 46 BDI patients, prior-year syndromal depression, but not prior-year syndromal mania/hypomania, was associated with poorer global, social, and work functioning (Goldberg and Harrow, 2011).

Several studies have associated not only syndromal, but also subsyndromal, depression with functional impairment in BD patients, and evidence suggests a dose-response relationship between depression severity and degree of functional impairment (Figure 3) (Altshuler et al., 2006; Bonnin et al., 2010; Goldberg and Harrow, 2011; Judd et al., 2005; Marangell et al., 2009; Solé et al., 2012). Subsyndromal manic/hypomanic symptoms, in contrast, have not consistently predicted poorer functional outcomes (Bonnin et al., 2010; Goldberg and Harrow, 2011; Judd et al., 2005). Moreover, in a study involving longitudinal follow-up of 85 BDI patients who achieved symptomatic recovery following a recent manic or hypomanic episode, residual depressive (but not manic/hypomanic) symptoms were associated with persistent functional impairment following symptomatic recovery, and longer delay from symptomatic to functional recovery (Gitlin et al., 2011).

Cognitive impairment, a consistent finding in studies of euthymic BD patients compared with healthy individuals, may be even more pronounced in the setting of depressive symptoms (Bourne et al., 2013; Kurtz and Gerraty, 2009). Thus, among 32 euthymic BDI and BDII patients, subthreshold depression (but not mood elevation) at baseline was the only significant predictor of worse cognitive functioning at 4-year follow-up (Bonnin et al., 2010). Likewise, in a meta-analysis of 31 studies involving 1276 euthymic BD patients, residual depressive (but not manic) symptoms were related to poorer performance on measures of memory, processing speed, and executive function (Bourne et al., 2013). However, the number of prior manic (but not prior depressive) episodes was associated with poorer cognitive performance on measures of verbal memory and processing speed (Bourne et al., 2013). Indeed, in a different meta-analysis of 60 studies assessing neurocognitive deficits in BD patients in different mood states (42 studies in euthymic, 13 in manic, and 5 in depressed patients), deficits in not only depressed but also manic patients were more pronounced than in euthymic patients, especially in verbal learning (Kurtz and Gerraty, 2009).

Quality of life, a measure reflecting subjective well-being across multiple life domains, has been consistently lower in BD patients than in the general population, and may even be lower than in unipolar MDD patients (Depp et al., 2006; Gutierrez-Rojas et al., 2008; Miller et al., 2013; Sierra et al., 2005; Yatham et al., 2004). Among 920 recently depressed BD patients, greater depression symptom severity was associated with reduced QOL across multiple domains (Yatham et al., 2004). Similarly, among the first 2000 participants in STEP-BD, those who were depressed at study entry had lower self-reported mental and overall QOL, compared not only with those who were manic/hypomanic, but also with those who were euthymic (Zhang et al., 2006). Similarly, other studies have confirmed the association of depression with reduced QOL in BD patients, whereas mania/hypomania is less consistently associated with lower QOL (Amini and Sharifi, 2012; Depp et al., 2006; Gutierrez-Rojas et al., 2008; Vojta et al., 2001). Taken together, the above findings suggest that persistent depressive symptoms of even subsyndromal

severity should be aggressively targeted to optimize patients' QOL and functioning.

8. Caregiver burden of bipolar depression

Bipolar depression can negatively affect not only BD patients but also their caregivers in terms of the temporal, financial, and emotional costs of providing care. Semistructured interviews of 500 primary caregivers for STEP-BD participants revealed that depressive (but not manic/hypomanic/mixed) episodes were associated with greater caregiver burden, even after controlling for longitudinal illness severity (days well in the prior year) (Ostacher et al., 2008). In a separate analysis of this sample, caregivers with higher, compared with lower, levels of self-reported burden reported more depression, poorer general health, and more chronic medical conditions, and contributed more financial resources to the patient during the prior year (Perlick et al., 2007). Indeed, generalized psychiatric distress, and increased symptoms of depression in particular, are consistent findings across studies assessing BD caregiver burden (Steele et al., 2010). These results clearly demonstrate that the profound impact of bipolar depression reaches beyond affected patients to those who care for them.

9. Suicide, suicide attempts, and burden of bipolar depression

In addition to immense burdens for family and significant others, attempted and completed suicides are associated with large economic costs, such as increased health service utilization and work productivity loss (due to attempted suicides) or workforce loss (due to completed suicides). Rates of attempted and completed suicide are considerably higher among patients with BD than in the general population. The estimated annual rates of attempted and completed suicide among BD patients are 3.9% and 1.4%, respectively, which are approximately one to two orders of magnitude greater than the corresponding general population rates (0.5% and 0.02%, respectively) (Baldessarini et al., 2006). BD patients are more likely than individuals in the general population to complete suicide attempts, as demonstrated by the higher ratio of completed to attempted suicide in BD (approximately 1:3) compared with the general population (1:20 to 1:40) (Baldessarini et al., 2006).

The depressive and mixed phases of bipolar illness, compared with pure manic states, carry substantially higher risk for suicide. Among 415 BD patients in the SFBN, those with a history of attempted suicide (compared with those without) had significantly greater duration and severity of depressive symptoms over a 1-year prospective follow-up (Leverich et al., 2006). In another study involving prospective follow-up of 176 BDI and BDII patients over a mean duration of 1.6 years, a total of 53 suicide attempts occurred (involving 20% of patients), all during depressive or mixed states (Valtonen et al., 2008). In this study, the incidence of suicide attempts was found to be 37-fold higher in mixed states and 18-fold higher in major depressive states compared with other phases of illness (Valtonen et al., 2008). Similarly, in a study involving 290 BDI and BDII patients, followed prospectively for a mean of 9.3 years, increased lifetime predominance of depressive recurrence and number of mixed episodes per year were significant risk factors for both suicidal ideation and suicide attempts (Undurraga et al., 2012b). These associations were further supported by findings in 928 BDI patients, among whom those with depression-predominant illness were significantly more likely to have attempted suicide, compared with patients with mania as their predominant polarity (Baldessarini et al., 2012). Taken together, these findings highlight the critical importance of effective treatment of depressive symptoms, whether occurring alone or in the context of concurrent mood elevation symptoms (i.e., mixed symptoms), to mitigate the increased risk of suicide in BD patients.

10. Polypharmacy in bipolar depression

Depressive symptoms in patients with BD are associated with prevalent use of antidepressants, which, in turn, may be associated with unfavorable (i.e., more challenging and costly) illness characteristics, including increases in rapid cycling, mixed symptoms, and suicidality (Ghaemi et al., 2003; Goldberg et al., 2007; Marangell et al., 2008; Undurraga et al., 2012a). Analysis of pharmacy claims for 7406 BD patients enrolled in a large commercial US health plan revealed that antidepressants were the most commonly prescribed class of initial medication regimens, despite limited evidence for their efficacy in BD (Baldessarini et al., 2008). In this study, one-third of patients were initially prescribed two or more psychotropic medications, and this proportion remained stable at 1-year follow-up (Baldessarini et al., 2008). Such polypharmacy (concurrent use of two or more prescription psychotropic medications) is increasingly common among BD patients and likely contributes to greater side-effect burden and economic costs for patients and society (Baldessarini et al., 2008; Frye et al., 2000; Goldberg et al., 2009). At the time of entry into the STEP-BD study, 68% of 4035 BD patients were prescribed two or more medications, 40% were prescribed three or more medications, and 18% took four or more medications (i.e., complex polypharmacy) (Goldberg et al., 2009). Patients with at least six lifetime depressive episodes and those with a history of attempted suicide were at increased risk for receiving complex pharmacotherapy (Goldberg et al., 2009). These findings highlight the contribution of the depressive phase of bipolar illness to the increased burden of polypharmacy among BD patients and underscore the challenges faced by clinicians in effectively treating patients with bipolar depression.

11. Management of burden associated with bipolar depression

In addition to aggressive pharmacological management of depressive symptoms, interventions that address the functional impairment and caregiver stress associated with bipolar depression are essential for mitigating the substantial burden associated with this illness. Functional and cognitive remediation strategies have shown promise for reduction of functional impairment in BD. In one study involving 239 euthymic BD patients, 21 weeks of functional remediation yielded significant improvement in overall functioning compared with treatment as usual, with particularly strong effects in interpersonal and occupational domains (Torrent et al., 2013). In another study, 18 BD patients with residual depressive symptoms received 14 sessions of cognitive remediation, which resulted in reduced depressive symptoms and improved occupational and psychosocial functioning, both immediately post-treatment and at 3 months' follow-up (Deckersbach et al., 2010). Psychosocial treatments as adjuncts to pharmacotherapy have also demonstrated efficacy in the amelioration of functional impairment in BD patients. Evidence-based approaches – including cognitive behavioral therapy, family-focused treatment, and interpersonal and social rhythm therapy – may yield improvements not only in long-term mood stability but also in social and family functioning and, potentially, vocational functioning (Miklowitz, 2011). Thus, interventions that target the functional deficits associated with bipolar depression, in conjunction with pharmacotherapies targeting depressive symptoms, may prove critical in reducing the burden of illness.

Management of caregiver burden is essential for ensuring the well-being of family and loved ones of individuals with BD,

particularly in light of evidence associating increased caregiver burden with poorer clinical outcomes for BD patients (Perlick et al., 2004) and the greater overall socioeconomic impact of BD (Dilsaver, 2011; Wyatt and Henter, 1995). One study compared a variation of family-focused treatment to a video-based health education intervention for 46 caregivers of patients with BD, finding that family-focused treatment was associated with significant reductions in caregiver depression and health risk behaviors, as well as decreased depression in patients (Perlick et al., 2010). Web-based informational resources (Berk et al., 2013) and peer support groups for families of patients with serious mental illness (Duckworth and Halpern, 2014) may also be of benefit in reducing caregiver burden.

12. Limitations of the study

This review, although comprehensive, provides a study-wise aggregate (rather than a patient-wise meta-analytic) summary of the relevant literature on this topic. The literature search was limited to the PubMed database and to English articles, potentially missing relevant non-English articles.

13. Conclusions

BD inflicts substantial burdens upon affected individuals, their caregivers, and society in general. Depressive symptoms are more pervasive than elevated/mixed symptoms in bipolar illness, and consequently account for more illness burden. Specifically, bipolar depressive compared with mood elevation symptoms incur greater indirect costs due to lost work productivity and increased rates of disability. Caregivers of patients with BD also experience greater burden due to depressive compared with mood elevation symptoms in terms of lost work productivity and general medical problems. In addition, syndromal and subsyndromal depression, as compared with mood elevation symptoms, yield greater impairments of overall functioning and QOL and are associated with increased risks of attempted and completed suicide. More aggressive and effective treatment of both syndromal and subsyndromal depressive symptoms in BD patients, combined with adjunctive interventions targeting the functional deficits associated with bipolar depression, are essential for alleviating the profound burden of this important aspect of this debilitating illness. Further studies investigating treatments for bipolar depression are warranted, and could benefit by including metrics not only for mood outcomes, but also for illness burden.

Disclosures

NUVIGIL (armodafinil) is not indicated for the treatment of major depression associated with bipolar I disorder. Teva conducted three Phase III studies. Based on an evaluation of the totality of results from all three studies, Teva has ceased development of and will not proceed with regulatory filings for Nuvigil (armodafinil) for the treatment of major depression associated with bipolar I disorder.

Conflict of interest

Dr. Miller received travel and accommodations compensation from the Agency for Healthcare Research and Quality for attendance at an investigators meeting in 2010. She also received a $1500 honorarium and travel and accommodations compensation from Pamlab, Inc. for attendance at an investigators meeting in 2011, and travel and accommodations compensation from Elan Pharmaceuticals for attendance at an investigators meeting in 2012.

Dr. Dell'Osso has served as a consultant and a speakers' bureau member for AstraZeneca. He has received grant/research support from Bristol-Myers Squibb, Cyberonics, and Lilly.

Dr. Ketter has served as a consultant to Allergan, Avanir, Bristol-Myers Squibb, Cephalon (now Teva), Forest, Janssen, Merck, Sunovion and Teva. He has received speaker fees from Abbott, AstraZeneca, GlaxoSmithKline, and Otsuka, and through Stanford University has received grants from AstraZeneca, Cephalon (now Teva), Lilly, Pfizer, and Sunovion. He received royalties from American Psychiatric Publishing. His spouse is employed by and owns stock in Janssen.

Funding/support

Funding for preliminary outline development and editorial review was provided by Teva Pharmaceuticals, North Wales, PA. Publication of this manuscript was supported by an independent medical education grant from Sunovion Pharmaceuticals, Marlborough, MA.

Contributor's statement

Shefali Miller and Terence Ketter managed the literature searches and analyses. Shefali Miller wrote the first draft of the manuscript. Bernardo Dell'Osso and Terence Ketter critically reviewed and revised the manuscript. All authors contributed to and have approved the final manuscript.

Acknowledgments

Development of a preliminary outline and editorial review and formatting of the manuscript was provided, under the direction of the authors, by Adrienne Drinkwater, PhD, and Patricia Johansen, PhD, Synchrony Medical Communications, LLC, West Chester, PA. This support was funded by Teva Pharmaceuticals, North Wales, PA. Publication of this manuscript was supported by an independent medical education grant from Sunovion Pharmaceuticals, Marlborough, MA.

Teva originated the idea and funded the development of this article. The decision to publish this article was solely the responsibility of the authors. All statements, opinions, and content presented in the published article are those of the authors and do not represent the opinions of Teva. Teva provided a medical accuracy review of the article.

References

Altshuler, L.L., Kupka, R.W., Hellemann, G., Frye, M.A., Sugar, C.A., McElroy, S.L., Nolen, W.A., Grunze, H., Leverich, G.S., Keck, P.E., Zermeno, M., Post, R.M., Suppes, T., 2010. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. Am. J. Psychiatry 167 (6), 708–715.

Altshuler, L.L., Post, R.M., Black, D.O., Keck, P.E., Jr., Nolen, W.A., Frye, M.A., Suppes, T., Grunze, H., Kupka, R.W., Leverich, G.S., McElroy, S.L., Walden, J., Mintz, J., 2006. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J. Clin. Psychiatry 67 (10), 1551–1560.

Amini, H., Sharifi, V., 2012. Quality of life in bipolar type I disorder in a one-year followup. Depress. Res Treat. 2012, 860745.

Baldessarini, R., Henk, H., Sklar, A., Chang, J., Leahy, L., 2008. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. Psychiatr. Serv. 59 (10), 1175–1183.

Baldessarini, R.J., Pompili, M., Tondo, L., 2006. Suicide in bipolar disorder: Risks and management. CNS Spectr. 11 (6), 465–471.

Baldessarini, R.J., Undurraga, J., Vazquez, G.H., Tondo, L., Salvatore, P., Ha, K., Khalsa, H.M., Lepri, B., Ha, T.H., Chang, J.S., Tohen, M., Vieta, E., 2012. Predominant recurrence polarity among 928 adult international bipolar I disorder patients. Acta Psychiatr. Scand. 125 (4), 293–302.

Berk, L., Berk, M., Dodd, S., Kelly, C., Cvetkovski, S., Jorm, A.F., 2013. Evaluation of the acceptability and usefulness of an information website for caregivers of people with bipolar disorder. BMC Med. 11, 162.

Bonnin, C.M., Martinez-Aran, A., Torrent, C., Pacchiarotti, I., Rosa, A.R., Franco, C., Murru, A., Sanchez-Moreno, J., Vieta, E., 2010. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. J. Affect. Disord. 121 (1–2), 156–160.

Bourne, C., Aydemir, O., Balanza-Martinez, V., Bora, E., Brissos, S., Cavanagh, J.T., Clark, L., Cubukcuoglu, Z., Dias, V.V., Dittmann, S., Ferrier, I.N., Fleck, D.E., Frangou, S., Gallagher, P., Jones, L., Kieseppa, T., Martinez-Aran, A., Melle, I., Moore, P.B., Mur, M., Pfennig, A., Raust, A., Senturk, V., Simonsen, C., Smith, D.J., Bio, D.S., Soeiro-de-Souza, M.G., Stoddart, S.D., Sundet, K., Szoke, A., Thompson, J.M., Torrent, C., Zalla, T., Craddock, N., Andreassen, O.A., Leboyer, M., Vieta, E., Bauer, M., Worhunsky, P.D., Tzagarakis, C., Rogers, R.D., Geddes, J.R., Goodwin, G.M., 2013. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr. Scand. 128 (3), 149–162.

Bryant-Comstock, L., Stender, M., Devercelli, G., 2002. Health care utilization and costs among privately insured patients with bipolar I disorder. Bipolar Disord. 4 (6), 398–405.

Calabrese, J.R., Hirschfeld, R.M., Frye, M.A., Reed, M.L., 2004. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. J. Clin. Psychiatry 65 (11), 1499–1504.

De Dios, C., Ezquiaga, E., Garcia, A., Soler, B., Vieta, E., 2010. Time spent with symptoms in a cohort of bipolar disorder outpatients in Spain: a prospective, 18-month follow-up study. J. Affect. Disord. 125 (1–3), 74–81.

Deckersbach, T., Nierenberg, A.A., Kessler, R., Lund, H.G., Ametrano, R.M., Sachs, G., Rauch, S.L., Dougherty, D., 2010. RESEARCH: Cognitive rehabilitation for bipolar disorder: An open trial for employed patients with residual depressive symptoms. CNS Neurosci. Ther. 16 (5), 298–307.

Dell'osso, B., Buoli, M., Bortolussi, S., Camuri, G., Vecchi, V., Altamura, A.C., 2011. Patterns of Axis I comorbidity in relation to age in patients with Bipolar Disorder: a cross-sectional analysis. J. Affect. Disord. 130 (1–2), 318–322.

Depp, C.A., Davis, C.E., Mittal, D., Patterson, T.L., Jeste, D.V., 2006. Health-related quality of life and functioning of middle-aged and elderly adults with bipolar disorder. J. Clin. Psychiatry 67 (2), 215–221.

Dilsaver, S.C., 2011. An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. J. Affect. Disord. 129 (1–3), 79–83.

Duckworth, K., Halpern, L., 2014. Peer support and peer-led family support for persons living with schizophrenia. Curr. Opin. Psychiatry 27 (3), 216–221.
Fiedorowicz, J.G., Palagummi, N.M., Forman-Hoffman, V.L., Miller, D.D., Haynes, W.G., 2008. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. Ann. Clin. Psychiatry 20 (3), 131–137.
Frye, M.A., Ketter, T.A., Leverich, G.S., Huggins, T., Lantz, C., Denicoff, K.D., Post, R.M., 2000. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J. Clin. Psychiatry 61 (1), 9–15.
Gadermann, A.M., Alonso, J., Vilagut, G., Zaslavsky, A.M., Kessler, R.C., 2012. Comorbidity and disease burden in the National Comorbidity Survey Replication (NCS-R). Depress. Anxiety 29 (9), 797–806.
Gardner, H.H., Kleinman, N.L., Brook, R.A., Rajagopalan, K., Brizee, T.J., Smeeding, J.E., 2006. The economic impact of bipolar disorder in an employed population from an employer perspective. J. Clin. Psychiatry 67 (8), 1209–1218.
Ghaemi, S.N., Hsu, D.J., Soldani, F., Goodwin, F.K., 2003. Antidepressants in bipolar disorder: the case for caution. Bipolar Disord. 5 (6), 421–433.
Gilbert, E., Marwaha, S., 2013. Predictors of employment in bipolar disorder: A systematic review. J. Affect. Disord. 145 (2), 156–164.
Gitlin, M.J., Mintz, J., Sokolski, K., Hammen, C., Altshuler, L.L., 2011. Subsyndromal depressive symptoms after symptomatic recovery from mania are associated with delayed functional recovery. J. Clin. Psychiatry 72 (5), 692–697.
Goes, F.S., McCusker, M.G., Bienvenu, O.J., Mackinnon, D.F., Mondimore, F.M., Schweizer, B., Depaulo, J.R., Potash, J.B., 2012. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. Psychol. Med. 42 (7), 1449–1459.
Goldberg, J.F., Brooks, J.O., III, Kurita, K., Hoblyn, J.C., Ghaemi, S.N., Perlis, R.H., Miklowitz, D.J., Ketter, T.A., Sachs, G.S., Thase, M.E., 2009. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. J. Clin. Psychiatry 70 (2), 155–162.
Goldberg, J.F., Harrow, M., 2011. A 15-year prospective follow-up of bipolar affective disorders: comparisons with unipolar nonpsychotic depression. Bipolar Disord. 13 (2), 155–163.
Goldberg, J.F., Perlis, R.H., Ghaemi, S.N., Calabrese, J.R., Bowden, C.L., Wisniewski, S., Miklowitz, D.J., Sachs, G.S., Thase, M.E., 2007. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. Am. J. Psychiatry 164 (9), 1348–1355.
Goldstein, B.I., Liu, S.M., Zivkovic, N., Schaffer, A., Chien, L.C., Blanco, C., 2011. The burden of obesity among adults with bipolar disorder in the United States. Bipolar Disord 13 (4), 387–395.
Goodwin, F.K., Jamison, K.R., 2007. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. 2nd ed. Oxford University Press, New York, NY.
Guo, J.J., Keck, P.E., Jr., Li, H., Jang, R., Kelton, C.M., 2008. Treatment costs and health care utilization for patients with bipolar disorder in a large managed care population. Value Health 11 (3), 416–423.
Guo, J.J., Keck, P.E., Li, H., Patel, N.C., 2007. Treatment costs related to bipolar disorder and comorbid conditions among Medicaid patients with bipolar disorder. Psychiatr. Serv. 58 (8), 1073–1078.
Gutierrez-Rojas, L., Gurpegui, M., Ayuso-Mateos, J.L., Gutierrez-Ariza, J.A., Ruiz-Veguilla, M., Jurado, D., 2008. Quality of life in bipolar disorder patients: a comparison with a general population sample. Bipolar Disord. 10 (5), 625–634.
Joffe, R.T., MacQueen, G.M., Marriott, M., Trevor, Y.L., 2004. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. Bipolar Disord. 6 (1), 62–66.
Judd, L.L., Akiskal, H.S., 2003. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J. Affect. Disord. 73 (1–2), 123–131.
Judd, L.L., Akiskal, H.S., Schettler, P.J., Coryell, W., Endicott, J., Maser, J.D., Solomon, D.A., Leon, A.C., Keller, M.B., 2003. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch. Gen. Psychiatry 60 (3), 261–269.
Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Leon, A.C., Solomon, D.A., Coryell, W., Maser, J.D., Keller, M.B., 2005. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch. Gen. Psychiatry 62 (12), 1322–1330.
Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., Keller, M.B., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry 59 (6), 530–537.
Kemp, D.E., Gao, K., Chan, P., Ganocy, S.J., Findling, R.L., Calabrese, J.R., 2010. Medical comorbidity in bipolar disorder: relationship between illnesses of the endocrine/metabolic system and treatment outcome. Bipolar Disord. 12 (4), 404–413.
Kessler, R.C., Akiskal, H.S., Ames, M., Birnbaum, H., Greenberg, P., Hirschfeld, R.M., Jin, R., Merikangas, K.R., Simon, G.E., Wang, P.S., 2006. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. Am. J. Psychiatry 163 (9), 1561–1568.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 62 (6), 593–602.
Kleinman, N.L., Brook, R.A., Rajagopalan, K., Gardner, H.H., Brizee, T.J., Smeeding, J.E., 2005. Lost time, absence costs, and reduced productivity output for employees with bipolar disorder. J. Occup. Environ. Med. 47 (11), 1117–1124.
Kupka, R.W., Altshuler, L.L., Nolen, W.A., Suppes, T., Luckenbaugh, D.A., Leverich, G.S., Frye, M.A., Keck, P.E., Jr., McElroy, S.L., Grunze, H., Post, R.M., 2007. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord. 9 (5), 531–535.
Kurtz, M.M., Gerraty, R.T., 2009. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology 23 (5), 551–562.
Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T., McElroy, S.L., Keck, P.E., Jr., Kupka, R.W., Denicoff, K.D., Nolen, W.A., Grunze, H., Martinez, M.I., Post, R.M., 2006. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am. J. Psychiatry 163 (2), 232–239.
Magalhaes, P.V., Kapczinski, F., Nierenberg, A.A., Deckersbach, T., Weisinger, D., Dodd, S., Berk, M., 2012. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr. Scand. 125 (4), 303–308.
Marangell, L.B., Dennehy, E.B., Miyahara, S., Wisniewski, S.R., Bauer, M.S., Rapaport, M.H., Allen, M.H., 2009. The functional impact of subsyndromal depressive symptoms in bipolar disorder: data from STEP-BD. J. Affect. Disord. 114 (1–3), 58–67.
Marangell, L.B., Dennehy, E.B., Wisniewski, S.R., Bauer, M.S., Miyahara, S., Allen, M.H., Martinez, M., Al Jurdi, R.K., Thase, M.E., 2008. Case-control analyses of the impact of pharmacotherapy on prospectively observed suicide attempts and completed suicides in bipolar disorder: findings from STEP-BD. J. Clin. Psychiatry 69 (6), 916–922.
Marsh, W.K., Ketter, T.A., Rasgon, N.L., 2009. Increased depressive symptoms in menopausal age women with bipolar disorder: age and gender comparison. J. Psychiatr. Res. 43 (8), 798–802.
McElroy, S.L., Altshuler, L.L., Suppes, T., Keck, P.E., Jr., Frye, M.A., Denicoff, K.D., Nolen, W.A., Kupka, R.W., Leverich, G.S., Rochussen, J.R., Rush, A.J., Post, R.M., 2001. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am. J. Psychiatry 158 (3), 420–426.
McIntyre, R.S., Konarski, J.Z., Misener, V.L., Kennedy, S.H., 2005. Bipolar disorder and diabetes mellitus: epidemiology, etiology, and treatment implications. Ann. Clin. Psychiatry 17 (2), 83–93.
McIntyre, R.S., Konarski, J.Z., Soczynska, J.K., Wilkins, K., Panjwani, G., Bouffard, B., Bottas, A., Kennedy, S.H., 2006. Medical comorbidity in bipolar disorder: implications for functional outcomes and health service utilization. Psychiatr. Serv. 57 (8), 1140–1144.
McMorris, B.J., Downs, K.E., Panish, J.M., Dirani, R., 2010. Workplace productivity, employment issues, and resource utilization in patients with bipolar I disorder. J. Med. Econ. 13 (1), 23–32.
Merikangas, K.R., Akiskal, H.S., Angst, J., Greenberg, P.E., Hirschfeld, R.M., Petukhova, M., Kessler, R.C., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 64 (5), 543–552.
Merikangas, K.R., Cui, L., Kattan, G., Carlson, G.A., Youngstrom, E.A., Angst, J., 2012. Mania with and without depression in a community sample of US adolescents. Arch. Gen. Psychiatry 69 (9), 943–951.
Merikangas, K.R., Jin, R., He, J.P., Kessler, R.C., Lee, S., Sampson, N.A., Viana, M.C., Andrade, L.H., Hu, C., Karam, E.G., Ladea, M., Medina-Mora, M.E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J.E., Zarkov, Z., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch. Gen. Psychiatry 68 (3), 241–251.
Miklowitz, D.J., 2011. Functional impairment, stress, and psychosocial intervention in bipolar disorder. Curr. Psychiatry Rep. 13 (6), 504–512.
Miller, C.J., Abraham, K.M., Bajor, L.A., Lai, Z., Kim, H.M., Nord, K.M., Goodrich, D.E., Bauer, M.S., Kilbourne, A.M., 2013. Quality of life among patients with bipolar disorder in primary care versus community mental health settings. J. Affect. Disord. 146 (1), 100–105.
Ostacher, M.J., Nierenberg, A.A., Iosifescu, D.V., Eidelman, P., Lund, H.G., Ametrano, R.M., Kaczynski, R., Calabrese, J., Miklowitz, D.J., Sachs, G.S., Perlick, D.A., 2008. Correlates of subjective and objective burden among caregivers of patients with bipolar disorder. Acta Psychiatr. Scand. 118 (1), 49–56.
Otto, M.W., Simon, N.M., Wisniewski, S.R., Miklowitz, D.J., Kogan, J.N., Reilly-Harrington, N.A., Frank, E., Nierenberg, A.A., Marangell, L.B., Sagduyu, K., Weiss, R.D., Miyahara, S., Thas, M.E., Sachs, G.S., Pollack, M.H., 2006. Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. Br. J. Psychiatry 189, 20–25.
Peele, P.B., Xu, Y., Kupfer, D.J., 2003. Insurance expenditures on bipolar disorder: clinical and parity implications. Am. J. Psychiatry 160 (7), 1286–1290.
Perlick, D.A., Miklowitz, D.J., Lopez, N., Chou, J., Kalvin, C., Adzhiashvili, V.,

Aronson, A., 2010. Family-focused treatment for caregivers of patients with bipolar disorder. Bipolar Disord. 12 (6), 627–637.
Perlick, D.A., Rosenheck, R.A., Clarkin, J.F., Maciejewski, P.K., Sirey, J., Struening, E., Link, B.G., 2004. Impact of family burden and affective response on clinical outcome among patients with bipolar disorder. Psychiatr. Serv. 55 (9), 1029–1035.
Perlick, D.A., Rosenheck, R.A., Miklowitz, D.J., Chessick, C., Wolff, N., Kaczynski, R., Ostacher, M., Patel, J., Desai, R., 2007. Prevalence and correlates of burden among caregivers of patients with bipolar disorder enrolled in the systematic treatment enhancement program for bipolar disorder. Bipolar Disord. 9 (3), 262–273.
Perlis, R.H., Miyahara, S., Marangell, L.B., Wisniewski, S.R., Ostacher, M., DelBello, M.P., Bowden, C.L., Sachs, G.S., Nierenberg, A.A., 2004. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry 55 (9), 875–881.
Post, R.M., Luckenbaugh, D.A., Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T., Keck, P.E., McElroy, S.L., Nolen, W.A., Kupka, R., Grunze, H., Walden, J., 2008. Incidence of childhood-onset bipolar illness in the USA and Europe. Br. J. Psychiatry 192 (2), 150–151.
Revicki, D.A., Matza, L.S., Flood, E., Lloyd, A., 2005. Bipolar disorder and health-related quality of life : review of burden of disease and clinical trials. Pharmacoeconomics 23 (6), 583–594.
Rosa, A.R., Reinares, M., Michalak, E.E., Bonnin, C.M., Sole, B., Franco, C., Comes, M., Torrent, C., Kapczinski, F., Vieta, E., 2010. Functional impairment and disability across mood states in bipolar disorder. Value Health 13 (8), 984–988.
Roshanaei-Moghaddam, B., Katon, W., 2009. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. Psychiatr. Serv. 60 (2), 147–156.
Shippee, N.D., Shah, N.D., Williams, M.D., Moriarty, J.P., Frye, M.A., Ziegenfuss, J.Y., 2011. Differences in demographic composition and in work, social, and functional limitations among the populations with unipolar depression and bipolar disorder: results from a nationally representative sample. Health Qual. Life Outcomes 9, 90.
Sierra, P., Livianos, L., Rojo, L., 2005. Quality of life for patients with bipolar disorder: relationship with clinical and demographic variables. Bipolar Disord. 7 (2), 159–165.
Simon, G.E., Bauer, M.S., Ludman, E.J., Operskalski, B.H., Unutzer, J., 2007. Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. J. Clin. Psychiatry 68 (8), 1237–1245.
Simon, G.E., Ludman, E.J., Unutzer, J., Operskalski, B.H., Bauer, M.S., 2008. Severity of mood symptoms and work productivity in people treated for bipolar disorder. Bipolar Disord. 10 (6), 718–725.
Solé, B., Bonnin, C.M., Torrent, C., Balanza-Martinez, V., Tabares-Seisdedos, R., Popovic, D., Martinez-Aran, A., Vieta, E., 2012. Neurocognitive impairment and psychosocial functioning in bipolar II disorder. Acta Psychiatr. Scand. 125 (4), 309–317.
Steele, A., Maruyama, N., Galynker, I., 2010. Psychiatric symptoms in caregivers of patients with bipolar disorder: a review. J. Affect. Disord. 121 (1-2), 10–21.
Stringaris, A., Santosh, P., Leibenluft, E., Goodman, R., 2010. Youth meeting symptom and impairment criteria for mania-like episodes lasting less than four days: an epidemiological enquiry. J. Child. Psychol. Psychiatry 51 (1), 31–38.
Torrent, C., Bonnin, C.M., Martinez-Aran, A., Valle, J., Amann, B.L., Gonzalez-Pinto, A., Crespo, J.M., Ibanez, A., Garcia-Portilla, M.P., Tabares-Seisdedos, R., Arango, C., Colom, F., Sole, B., Pacchiarotti, I., Rosa, A.R., Ayuso-Mateos, J.L., Anaya, C., Fernandez, P., Landin-Romero, R., Alonso-Lana, S., Ortiz-Gil, J., Segura, B., Barbeito, S., Vega, P., Fernandez, M., Ugarte, A., Subira, M., Cerrillo, E., Custal, N., Menchon, J.M., Saiz-Ruiz, J., Rodao, J.M., Isella, S., Alegria, A., Al-Halabi, S., Bobes, J., Galvan, G., Saiz, P.A., Balanza-Martinez, V., Selva, G., Fuentes-Dura, I., Correa, P., Mayoral, M., Chiclana, G., Merchan-Naranjo, J., Rapado-Castro, M., Salamero, M., Vieta, E., 2013. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. Am. J. Psychiatry 170 (8), 852–859.
Undurraga, J., Baldessarini, R.J., Valenti, M., Pacchiarotti, I., Tondo, L., Vazquez, G., Vieta, E., 2012a. Bipolar depression: clinical correlates of receiving antidepressants. J. Affect. Disord. 139 (1), 89–93.
Undurraga, J., Baldessarini, R.J., Valenti, M., Pacchiarotti, I., Vieta, E., 2012b. Suicidal risk factors in bipolar I and II disorder patients. J. Clin. Psychiatry 73 (6), 778–782.
Valtonen, H.M., Suominen, K., Haukka, J., Mantere, O., Leppamaki, S., Arvilommi, P., Isometsa, E.T., 2008. Differences in incidence of suicide attempts during phases of bipolar I and II disorders. Bipolar Disord. 10 (5), 588–596.
Vancampfort, D., Vansteelandt, K., Correll, C.U., Mitchell, A.J., De Herdt A., Sienaert, P., Probst, M., De Hert M., 2013. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Am. J. Psychiatry 170 (3), 265–274.
Vojta, C., Kinosian, B., Glick, H., Altshuler, L., Bauer, M.S., 2001. Self-reported quality of life across mood states in bipolar disorder. Compr. Psychiatry 42 (3), 190–195.
Weber, N.S., Fisher, J.A., Cowan, D.N., Niebuhr, D.W., 2011. Psychiatric and general medical conditions comorbid with bipolar disorder in the National Hospital Discharge Survey. Psychiatr. Serv. 62 (10), 1152–1158.
Weiss, R.D., Ostacher, M.J., Otto, M.W., Calabrese, J.R., Fossey, M., Wisniewski, S.R., Bowden, C.L., Nierenberg, A.A., Pollack, M.H., Salloum, I.M., Simon, N.M., Thase, M.E., Sachs, G.S., 2005. Does recovery from substance use disorder matter in patients with bipolar disorder? J. Clin. Psychiatry 66 (6), 730–735.
Westman, J., Hallgren, J., Wahlbeck, K., Erlinge, D., Alfredsson, L., Osby, U., 2013. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. BMJ Open 3 (4).
Williams, M.D., Shah, N.D., Wagie, A.E., Wood, D.L., Frye, M.A., 2011. Direct costs of bipolar disorder versus other chronic conditions: an employer-based health plan analysis. Psychiatr. Serv. 62 (9), 1073–1078.
World Health Organization, 2008. The global burden of disease: 2004 update. Geneva, Switzerland, World Health Organization, http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed October 17, 2014.
Wyatt, R.J., Henter, I., 1995. An economic evaluation of manic-depressive illness--1991. Soc. Psychiatry Psychiatr. Epidemiol. 30 (5), 213–219.
Yatham, L.N., Lecrubier, Y., Fieve, R.R., Davis, K.H., Harris, S.D., Krishnan, A.A., 2004. Quality of life in patients with bipolar I depression: data from 920 patients. Bipolar Disord. 6 (5), 379–385.
Zhang, H., Wisniewski, S.R., Bauer, M.S., Sachs, G.S., Thase, M.E., 2006. Comparisons of perceived quality of life across clinical states in bipolar disorder: data from the first 2000 Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) participants. Compr. Psychiatry 47 (3), 161–168.
Zimmerman, M., Galione, J.N., Chelminski, I., Young, D., Dalrymple, K., Ruggero, C.J., 2010. Sustained unemployment in psychiatric outpatients with bipolar disorder: frequency and association with demographic variables and comorbid disorders. Bipolar Disord. 12 (7), 720–726.