ECONOMIC BURDEN OF BIPOLAR DISORDER TYPE I (BD-I) IN THE US: A SYSTEMATIC REVIEW OF THE LITERATURE

Greene M[1], Clark OAC[2], Paladini L[2], Touya M[3]

[1]Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA,
[2]Evidencias - Kantar Health, Campinas, Brazil, [3]Lundbeck, Deerfield, IL, USA

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BACKGROUND

- Bipolar disorder (BD) is one of the leading causes of disability secondary to mental/behavior disorders worldwide, especially because of its early age of onset, elevated relapse rates and high rate of comorbid conditions.
- Bipolar Disorder type I (BD-I) is a chronic and severe mental illness characterized by at least one manic episode with the possibility of other major depressive or hypomanic episodes.

OBJECTIVES

The goals of this systematic (SR) review of the literature were to evaluate the following aspects of BD in the United States (US):

- financial costs (direct and indirect) imposed by the disease
- impact of specific pharmacological treatments on costs
- impact of BD on employability and work performance (presenteeism and absenteeism)
- impact of BD on Health-Related Quality of Life (HRQOL) in comparison to controls
- evolution of HRQOL during the course-of-illness (including changes secondary to specific pharmacological treatments)

METHODS

- A comprehensive search was performed in Medline and EMBASE (2006 to 2016) for studies addressing the aspects described above.
- Inclusion criteria:
  - studies enrolled US patients
  - data were collected or papers published after year 2000 so the results could more closely mirror current standards of care
  - patients should be euthymic, in a manic or mixed episode, or recovering after a manic or mixed episode
- Exclusion criteria:
  - studies focused on patients enrolled after a depressive episode

Figure 1. Search Strategies

Cost of illness

SR in MEDLINE: *("Bipolar Disorder"[Mesh] OR (bipolar AND disorder)) AND "Costs and Cost Analysis"[Mesh] AND systematic[sb].* For studies published after the most updated SR (**Complement**): ("Bipolar Disorder"[Mesh] OR (bipolar AND disorder)) AND "Costs and Cost Analysis"[Mesh]

SR in EMBASE: ('bipolar disorder'/exp or 'bipolar disorder') and (('cost of illness'/exp or 'cost of illness')

Impact of BD over employability and work productivity

SR in MEDLINE: *("Bipolar Disorder"[Mesh] OR (bipolar AND disorder)) AND (employment OR unemployment OR absenteeism OR presenteeism' OR workplace OR productivity OR work functioning OR work disability OR sick leave) AND systematic[sb].* **Complement:** ("Bipolar Disorder"[Mesh] OR (bipolar AND disorder)) AND (employment OR unemployment OR absenteeism OR presenteeism' OR workplace OR productivity OR work functioning OR work disability OR sick leave)

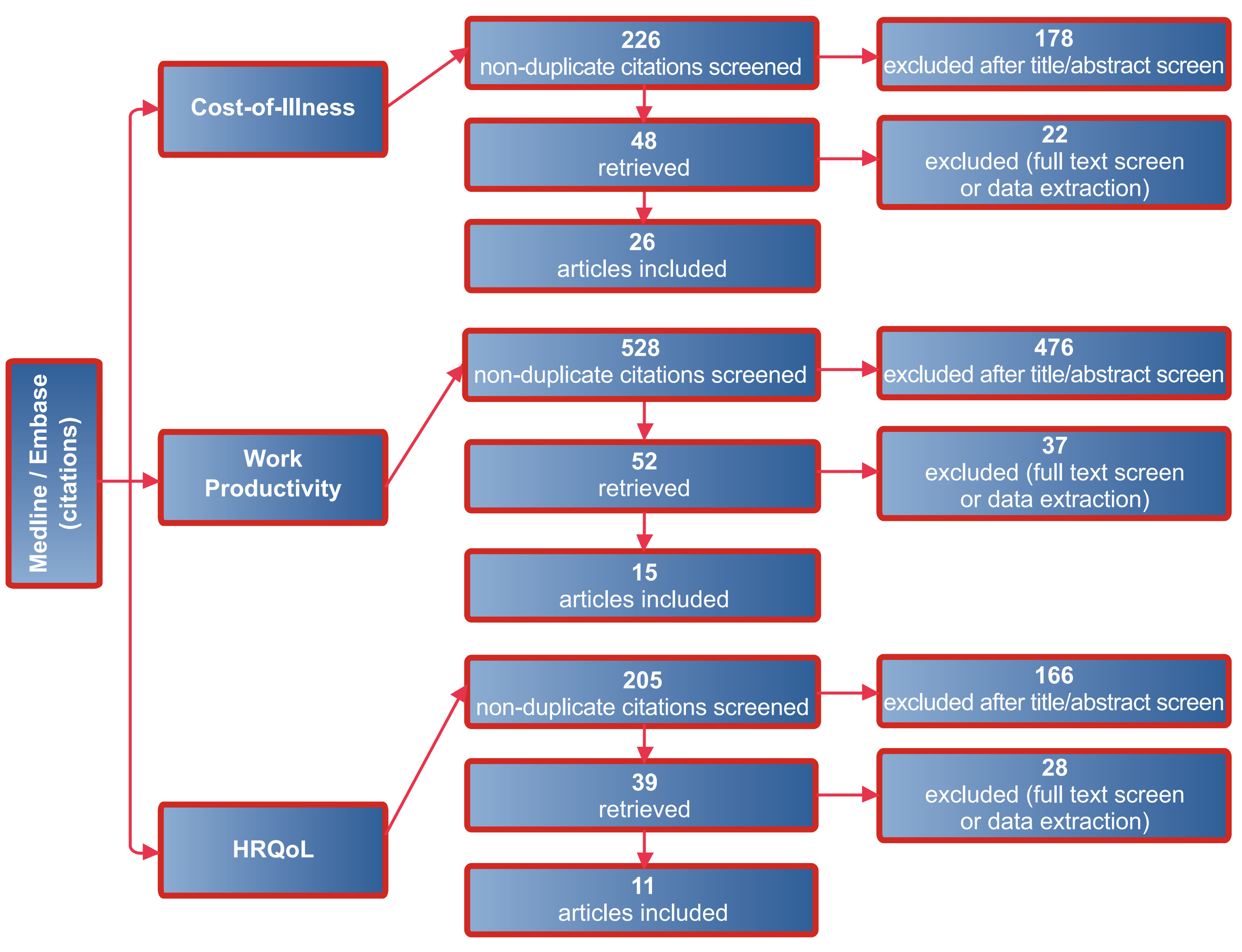
SR in EMBASE: ('bipolar disorder'/exp or 'bipolar disorder') and ('employment'/exp OR 'employment' OR 'unemployment'/exp OR 'unemployment' OR 'absenteeism'/exp OR 'absenteeism' OR 'presenteeism'/exp OR 'presenteeism' OR 'workplace'/exp OR 'workplace' OR 'productivity'/exp OR 'productivity' OR 'work functioning'/exp OR 'work functioning' OR 'work disability'/exp OR 'work functioning' OR 'sick leave'/exp OR 'sick leave')

Health-Related Quality-of-Life

SR in MEDLINE: *("Bipolar Disorder"[Mesh] OR (bipolar AND disorder)) AND (quality of life OR "Quality of Life"[Mesh] OR sf-36 OR sf-12 OR eq-5d) AND systematic[sb].* **Complement:** ("Bipolar Disorder"[Mesh] OR (bipolar AND disorder)) AND (prospective OR naturalistic OR longitudinal) AND (quality of life OR "Quality of Life"[Mesh] OR sf-36 OR sf-12 OR eq-5d)

SR in EMBASE: (('bipolar disorder'/exp or 'bipolar disorder') and ('quality of life'/exp or 'quality of life'))

Figure 2. Prisma Flow Diagram


Medline / Embase (citations)
Cost-of-Illness
226
non-duplicate citations screened
178
excluded after title/abstract screen
48
retrieved
22
excluded (full text screen or data extraction)
26
articles included
Work Productivity
528
non-duplicate citations screened
476
excluded after title/abstract screen
52
retrieved
37
excluded (full text screen or data extraction)
15
articles included
HRQoL
205
non-duplicate citations screened
166
excluded after title/abstract screen
39
retrieved
28
excluded (full text screen or data extraction)
11
articles included

RESULTS

Cost-of-illness

- 26 studies were included [1-26]
- Main reasons for exclusion: lack of US patients, lack of specific data on BD, older data (collected before year 2000), study design and analysis only for patients with BD specific features (e.g.: depression).
- Annual societal costs per patient with BD varied from $1,904 to $33,090, with productivity losses making up to 20%-94% of costs.
- Overall direct healthcare costs ranged from $8,000-$14,000 per patient purchasing parity power.
- Total annual health care costs were higher for patients with BD than for those without the disease ($12,764 vs $3,140 per patients per year).
- Improved adherence to medication was related to lower medical costs in BD (1-point increment in MPR reduced $123-$439 in mental health expenditures per patients with manic/mixed symptoms receiving antipsychotics per year).

RESULTS

Employability & Work Productivity

- 15 studies were included [4,9,16,27-38]
- Main reasons for exclusion: lack of US patients, lack of specific data on BD, older data (collected before year 2000), studies not addressing the impact of BD over employment or work functioning (e.g.: predictors of employment) and studies addressing only the impact of specific patient characteristics over employment or productivity (e.g.: cognition, comorbid diabetes, comorbid personality disorders).
- 40% to 60% of patients with BD were employed, with higher employment rates during early phases of disease compared to later stages.
- Mean annual absence costs per patient (sick leave, short/long-term disability, and workers' compensation) were significantly higher for employers of patients with BD when compared with those without the disease ($1,995 vs $885).
- See the main results for studies in this category listed below.

MAIN RESULTS OF STUDIES EVALUATING EMPLOYABILITY AND WORK PRODUCTIVITY IN PATIENTS WITH BD

Absenteeism and presenteeism

- Employees with BD had 18.9 days of work absence per year vs. 7.4 days for those without BD. Gardner 2006 [9*].
- Employees with BD were less likely to be present at work. Absence rates over 1 year resulted in significant productivity losses. Kleinman 2005 [16*].
- BD related absenteeism was 27.7 days and BD related presenteeism was 35.3 days. Kessler 2006 [33].
- Patients with BD not working/studying: 47.2%. Missed days at work: 8.36 (average) Shippee 2011 [37].

Proportion of employed / unemployed patients

- In one study 60% of patients with BD-I were employed at baseline, but only 31% remained so at 52 weeks. Chengappa 2005 [28].
- An observational study showed that 46.6% of patients with BD-I were employed at baseline and termination while 30.4% were unemployed. Gilbert 2010 [30].
- In another study, the proportions of patients with BD employed were: 66% (baseline), 64% (6 months), 63% (12 months) and 62% (24 months). Simon 2008 [38].
- For patients with BD hospitalized early in the illness: 54% worked/studied full-time at 6 months and 21% part-time. Dickerson 2010 [29].
- Employment status for patients with BD: full-time (25%), part-time (16%), unemployed (41%), retired (17%), student (1%) Hirschfeld 2003 [32].
- The mean performance as worker, homemaker or student (Strauss and Carpenter 5-point scale) for young adults living with BD was 2.4 (at 2 years); 2.5 (at 4.5 years) and 2.6 (at 7-8 years). Goldberg 2005 [31].
- BD has "complex, varied and intermittent effects" on work functioning, so it is necessary to develop appropriate measures of occupational functioning among these patients. Michalak 2007 [36].

Costs

- A cost analysis study comparing before and after BD treatment showed reductions in direct medical costs after starting treatment, specially for the cohort receiving atypical AP only. Brook 2007 [27].
- Accurate and timely recognition of BD was associated with lower costs due to work loss. Birnbaum 2003 [4].

Health-Related Quality-of-Life

- 11 studies were included [39-49]
- Main reasons for exclusion: lack of US patients, lack of specific data on BD, older data (collected before year 2000), studies not addressing measures of QoL or utility by validated tools (e.g.: SF-36, SF-12, EQ-5D, Q-LES-Q-SF), studies addressing specific BD populations (e.g.: patients with comorbidities).
- HRQOL is impaired in patients with BD compared with healthy individuals and with patients diagnosed with other chronic psychiatric and medical conditions.
- BD pharmacological and non-pharmacological treatments have a positive effect on HRQOL.
- See the main results for studies in this category listed below.

MAIN RESULTS OF STUDIES EVALUATING HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH BD

- Physical Component Scores (PCS) worsened with age while Mental Component Scores (MCS) tended to improve in older patients with BD. Fenn 2005 [40].
- Youths with BD and their caregivers had lower HRQOL compared to youths with asthma, obesity, atopic dermatitis, and chronic depression. Freeman 2009 [41].
- Short and long sleep duration were associated with poorer function and QoL compared to normal sleepers. Gruber 2009 [42].
- Illicit drug use adversely affected mental HRQOL while increased number of medical comorbidities negatively affected physical HRQOL. Kilbourne 2009 [44].
- Patients with BD receiving adjunctive olanzapine had greater improvement in HRQOL compared to the placebo group. Namjoshi 2004 [46].
- No statistically significant differences were found in HRQOL for patients with BD treated with olanzapine or divalproex Revicki 2003 [47].
- Depressive symptoms significantly related to impaired HRQOL. Higher scores were achieved by patients in euthymia. Zhang 2006 [49].
- Treatment with lithium or quetiapine was associated with significant improvements in HRQOL, regardless of the drug used. Deckersbach 2016 [39].
- BD carries a substantial burden in HRQOL especially in the mental domains. Significant improvements in HRQOL were seen with asenapine vs olanzapine and placebo in patients with mixed episodes. Michalak 2014 [45].
- There is a double burden of aging and disease in patients with BD. Weisenbach 2014 [48].

*These studies comprise the same populations but report different analysis.

CONCLUSIONS

- When compared with other populations, patients with BD imposed higher medical costs for payers.
- However, treatment adherence was associated with reduced health expenditures.
- Both employability and work productivity were negatively affected by the disease, as was HRQoL.

LIMITATIONS

- Regarding cost of illness analysis, impact on employment and work productivity and quality of life assessments, there is scarce data specific for patients with BD-I (most studies include patients with BD as a group).
- Quality-of-life impact resulting from treatment has been addressed mainly in short-duration studies (up to 12 weeks of follow-up). There is also need for long-term studies addressing the evolution of HRQOL in BD patients.

References

1. Bagalman E, Muser E, Choi JC, et al. Health care resource utilization and costs in a commercially insured population of patients with bipolar disorder type I and frequent psychiatric interventions. Clin Ther. 2011;33(10):1381-1390 e1384.
2. Bergeson JG, Kalsekar I, Jing Y, You M, Forbes RA, Hebden T. Medical care costs and hospitalization in patients with bipolar disorder treated with atypical antipsychotics. Am Health Drug Benefits. 2012;5(6):379-386.
3. Berry EA, Heaton PT, Kelton CM. National estimates of the inpatient burden of pediatric bipolar disorder in the United States. J Ment Health Policy Econ. 2011;14(3):115-123.
4. Birnbaum HG, Shi L, Dial E, Oster EF, Greenberg PE, Mallett DA. Economic consequences of not recognizing bipolar disorder patients: a cross-sectional descriptive analysis. J Clin Psychiatry. 2003;64(10):1201-1209.
5. Brook RA, Rajagopalan K, Kleinman NL, Smeeding JE, Brizee TJ, Gardner HH. Incurring greater health care costs: risk stratification of employees with bipolar disorder. Prim Care Companion J Clin Psychiatry. 2006;8(1):17-24.
6. Busch AB, Yoon F, Barry CL, et al. The effects of mental health parity on spending and utilization for bipolar, major depression, and adjustment disorders. Am J Psychiatry. 2013;170(2):180-187.
7. Centorrino F, Mark TL, Talamo A, Oh K, Chang J. Health and economic burden of metabolic comorbidity among individuals with bipolar disorder. J Clin Psychopharmacol. 2009;29(6):595-600.
8. Durden E, Bagalman E, Muser E, et al. Characteristics, healthcare utilization and costs of bipolar disorder type I patients with and without frequent psychiatric intervention in a Medicaid population. J Med Econ. 2010;13(4):698-704.
9. Gardner HH, Kleinman NL, Brook RA, Rajagopalan K, Brizee TJ, Smeeding JE. The economic impact of bipolar disorder in an employed population from an employer perspective. J Clin Psychiatry. 2006;67(8):1209-1218.
10. Gianfrancesco FD, Sajatovic M, Rajagopalan K, Wang RH. Antipsychotic treatment adherence and associated mental health care use among individuals with bipolar disorder. Clin Ther. 2008;30(7):1358-1374.
11. Guo JJ, Keck PE, Jr., Li H, Jang R, Kelton CM. Treatment costs and health care utilization for patients with bipolar disorder in a large managed care population. Value Health. 2008;11(3):416-423.
12. Harley C, Li H, Corey-Lisle P, L'Italien GJ, Carson W. Influence of medication choice and comorbid diabetes: the cost of bipolar disorder in a privately insured US population. Soc Psychiatry Psychiatr Epidemiol. 2007;42(9):690-697.
13. Jiang Y, Ni W. Estimating the Impact of Adherence to and Persistence with Atypical Antipsychotic Therapy on Health Care Costs and Risk of Hospitalization. Pharmacotherapy. 2015;35(9):813-822.
14. Jin H, McCrone P. Cost-of-illness studies for bipolar disorder: systematic review of international studies. Pharmacoeconomics. 2015;33(4):341-353.
15. Kleine-Budde K, Touil E, Moock J, Bramesfeld A, Kawohl W, Rossler W. Cost of illness for bipolar disorder: a systematic review of the economic burden. Bipolar Disord. 2014;16(4):337-353.
16. Kleinman NL, Brook RA, Rajagopalan K, Gardner HH, Brizee TJ, Smeeding JE. Lost time, absence costs, and reduced productivity output for employees with bipolar disorder. J Occup Environ Med. 2005;47(11):1117-1124.
17. Knoth RL, Chen K, Tafesse E. Datapoints: Costs associated with the treatment of patients with bipolar disorder in a managed care organization. Psychiatr Serv. 2004;55(12):1353.
18. Locklear JC, Alemayehu B, Brody RS, et al. Treatment patterns, healthcare resource utilization and costs in patients with bipolar disorder, newly treated with extended release or immediate release quetiapine fumarate using US healthcare administrative claims data. Clin Ther. 2013;35(12):1923-1932.
19. Ohsfeldt RL, Lage MJ, Rajagopalan K. Medication use, service utilization, and medical costs associated with new episodes of bipolar disorder: evidence from a retrospective claims database. Prim Care Companion J Clin Psychiatry. 2007;9(4):280-286.
20. Qiu Y, Christensen DB, Fu AZ, Liu GG. Cost analysis in a Medicaid program for patients with bipolar disorder who initiated atypical antipsychotic monotherapy. Curr Med Res Opin. 2009;25(2):351-361.
21. Rajagopalan K, Kleinman NL, Brook RA, Gardner HH, Brizee TJ, Smeeding JE. Costs of physical and mental comorbidities among employees: a comparison of those with and without bipolar disorder. Curr Med Res Opin. 2006;22(3):443-452.
22. Seabury SA, Goldman DP, Kalsekar I, Sheehan JJ, Laubmeier K, Lakdawalla DN. Formulary restrictions on atypical antipsychotics: impact on costs for patients with schizophrenia and bipolar disorder in Medicaid. Am J Manag Care. 2014;20(2):e52-60.
23. Stang PE, Frank C, Kalsekar A, Yood MU, Wells K, Burch S. The clinical history and costs associated with delayed diagnosis of bipolar disorder. MedGenMed. 2006;8(2):18.
24. Stensland MD, Jacobson JG, Nyhuis A. Service utilization and associated direct costs for bipolar disorder in 2004: an analysis in managed care. J Affect Disord. 2007;101(1-3):187-193.
25. Williams MD, Shah ND, Wagie AE, Wood DL, Frye MA. Direct costs of bipolar disorder versus other chronic conditions: an employer-based health plan analysis. Psychiatr Serv. 2011;62(9):1073-1078.
26. Guo JJ, Keck PE, Li H, Patel NC. Treatment costs related to bipolar disorder and comorbid conditions among Medicaid patients with bipolar disorder. Psychiatr Serv. 2007;58(8):1073-1078.
27. Brook RA, Kleinman NL, Rajagopalan K. Employee costs before and after treatment initiation for bipolar disorder. Am J Manag Care. 2007;13(4):179-186.
28. Chengappa KN, Hennen J, Baldessarini RJ, et al. Recovery and functional outcomes following olanzapine treatment for bipolar I mania. Bipolar Disord. 2005;7(1):68-76.
29. Dickerson F, Origoni A, Stallings C, Khushalani S, Dickinson D, Medoff D. Occupational status and social adjustment six months after hospitalization early in the course of bipolar disorder: a prospective study. Bipolar Disord. 2010;12(1):10-20.
30. Gilbert AM, Olino TM, Houck P, Fagiolini A, Kupfer DJ, Frank E. Self-reported cognitive problems predict employment trajectory in patients with bipolar I disorder. J Affect Disord. 2010;124(3):324-328.
31. Goldberg JF, Harrow M. Subjective life satisfaction and objective functional outcome in bipolar and unipolar mood disorders: a longitudinal analysis. J Affect Disord. 2005;89(1-3):79-89.
32. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry. 2003;64(2):161-174.
33. Kessler RC, Akiskal HS, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. Am J Psychiatry. 2006;163(9):1561-1568.
34. Laxman KE, Lovibond KS, Hassan MK. Impact of bipolar disorder in employed populations. Am J Manag Care. 2008;14(11):757-764.
35. Marwaha S, Durrani A, Singh S. Employment outcomes in people with bipolar disorder: a systematic review. Acta Psychiatr Scand. 2013;128(3):179-193.
36. Michalak EE, Yatham LN, Maxwell V, Hale S, Lam RW. The impact of bipolar disorder upon work functioning: a qualitative analysis. Bipolar Disord. 2007;9(1-2):126-143.
37. Shippee ND, Shah ND, Williams MD, Moriarty JP, Frye MA, Ziegenfuss JY. 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. 2011;9:90.
38. Simon GE, Ludman EJ, Unutzer J, Operskalski BH, Bauer MS. Severity of mood symptoms and work productivity in people treated for bipolar disorder. Bipolar Disord. 2008;10(6):718-725.
39. Deckersbach T, Nierenberg AA, McInnis MG, et al. Baseline disability and poor functioning in bipolar disorder predict worse outcomes: results from the Bipolar CHOICE study. J Clin Psychiatry. 2016;77(1):100-108.
40. Fenn HH, Bauer MS, Altshuler L, et al. Medical comorbidity and health-related quality of life in bipolar disorder across the adult age span. J Affect Disord. 2005;86(1):47-60.
41. Freeman AJ, Youngstrom EA, Michalak E, Siegel R, Meyers OI, Findling RL. Quality of life in pediatric bipolar disorder. Pediatrics. 2009;123(3):e446-452.
42. Gruber J, Harvey AG, Wang PW, et al. Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Affect Disord. 2009;114(1-3):41-49.
43. IsHak WW, Brown K, Aye SS, Kahloon M, Mobaraki S, Hanna R. Health-related quality of life in bipolar disorder. Bipolar Disord. 2012;14(1):6-18.
44. Kilbourne AM, Perron BE, Mezuk B, Welsh D, Ilgen M, Bauer MS. Co-occurring conditions and health-related quality of life in patients with bipolar disorder. Psychosom Med. 2009;71(8):894-900.
45. Michalak EE, Guiraud-Diawara A, Sapin C. Asenapine treatment and health-related quality of life in patients experiencing bipolar I disorder with mixed episodes: post-hoc analyses of pivotal trials. Curr Med Res Opin. 2014;30(4):711-718.
46. Namjoshi MA, Risser R, Shi L, Tohen M, Breier A. Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid. J Affect Disord. 2004;81(3):223-229.
47. Revicki DA, Paramore LC, Sommerville KW, Swann AC, Zajecka JM. Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes. J Clin Psychiatry. 2003;64(3):288-294.
48. Weisenbach SL, Marshall D, Weldon AL, et al. The double burden of age and disease on cognition and quality of life in bipolar disorder. Int J Geriatr Psychiatry. 2014;29(9):952-961.
49. Zhang H, Wisniewski SR, Bauer MS, Sachs GS, Thase ME. 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. 2006;47(3):161-168.

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FOR FURTHER INFORMATION: Please contact – Malik Greene (Mallik.Greene@otsuka-us.com)