Review article

Unrecognized bipolar disorder in patients with depression managed in primary care: A systematic review and meta-analysis[☆],[☆☆]

John Daveney[a], Maria Panagioti[b],[*], Waquas Waheed[b], Aneez Esmail[a]

[a] NIHR School for Primary Care Research, Manchester Academic Health Science Centre, University of Manchester, M13 9PL, UK
[b] NIHR School for Primary Care Research, NIHR Greater Manchester Patient Safety Translational Research Centre, Manchester Academic Health Science Centre, University of Manchester, M13 9PL, UK

ARTICLE INFO

ABSTRACT

Purpose: Bipolar disorder is a common, severe mental health condition and a major financial burden for healthcare systems across the globe. There is some evidence that unrecognized bipolar disorder is prevalent amongst patients with depression in primary care which can lead to non-optimal treatment. However, a systematic synthesis of this literature is lacking. We aimed to determine the percentage of primary care patients who are diagnosed with depression that have unrecognized bipolar disorder.

Methods: Medline, Embase, Cochrane and PsycINFO were searched to January 2019. We included quantitative observational studies. Risk of bias was assessed using the Newcastle Ottawa cohort scale. Analyses were performed using random-effects models, heterogeneity was quantified using I^2 and formal tests of publication bias were undertaken.

Results: Ten studies with 3803 participants with depression in primary care were included. The pooled prevalence of bipolar disorder in those with depression was 17% (95% CI = 12 to 22). The prevalence of unrecognized bipolar depression was higher in studies which used questionnaires as assessment tools for bipolar disorder compared to studies which used clinical interviews but this difference was not significant (14%, 95% CI = 8 to 20 versus 22%, 95% CI = 16 to 28, Q = 1.27, p = 0.12). The prevalence of unrecognized bipolar disorder was not significantly affected by study-level variations in the risk of bias and we found no evidence for publication bias.

Conclusion: Over 3 in 20 patients with depression have unrecognized bipolar disorder in primary care which can lead to harmful patient outcomes. Increased awareness of unrecognition of bipolar disorder in primary care patients with depression and efficient assessment strategies in primary care are warranted.

1. Introduction

Bipolar disorder is a chronic condition, characterized by alternating episodes of mania and depression [1]. It comprises a spectrum defined by the severity and duration of mood elevation, from bipolar II (hypomania) to bipolar I (full episodes of mania) to bipolar with psychosis [1]. It is the 6th leading cause of disability worldwide [2,3] with a prevalence of up to 5% [4,5]. An increase in the number of people with bipolar disorder by 49.1% globally has been observed between 1990 and 2013, accounted for by increasing population and ageing [3]. The

annual costs for bipolar disorder exceeds $45 billion in the US and $3 billion in the UK excluding lost employment [6,7].

Nearly 90% of people with depression in the UK are treated in primary care only, while the percentage of US patients with depression treated in a general medical setting is 73.3% [8,9]. There is growing evidence that a considerable percentage of primary care patients with depression have unrecognized bipolar disorder [10–13]. The identification of unrecognized cases of bipolar disorder amongst patients with depression is crucial for appropriate pharmacological management. Antidepressant monotherapy is non-optimal for patients with bipolar

disorder and can lead to adverse outcomes including an increased risk of mania or hypomania and suicide [13–17].

At present, there is no up-to-date evidence concerning the prevalence of unrecognized bipolar disorder in primary care patients diagnosed with depression; this study aims to address this gap.

2. Methods

This systematic review was conducted and reported in accordance with the Reporting Checklist for Meta-analyses of Observational Studies (MOOSE) [18] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [19]. The completed MOOSE checklist is available in the appendix (eTable 1).

2.1. Search strategy

Computerized literature searches of the OVID Medline, Embase, Cochrane library and PsycINFO databases were conducted from inception to 10th January 2019. No limitations were set on the language of publication. The search strategy is provided in the appendix (eTable 2). Sensitivity searches were also conducted in Google Scholar using the 'Advanced search' function to find all articles related to prevalence rates with the terms 'misdiagnosis' 'unrecognized' and 'bipolar' in their title. Moreover, we searched the reference lists of the eligible studies, previous systematic reviews and conducted a forward citation search for eligible studies.

2.2. Eligibility criteria

- Population: Adult patients diagnosed with depression, with no prior diagnosis of, or treatment for bipolar disorder.
- Outcomes: prevalence rates of unrecognized bipolar disorder in depressed patients.
- Study design: Quantitative observational studies including cross-sectional, retrospective and prospective cohort studies.
- Context: Primary care settings in any country. Papers published in peer-reviewed journals.
- Exclusions: general adult psychiatric (non-primary care) populations or studies involving children or adolescents. We also excluded grey literature.

2.3. Study selection and data extraction

The hits of the searches were exported to an endnote file and duplicates were removed. Titles and abstracts were screened for relevance. Next, full-texts were assessed and screened using our eligibility criteria. A structured Excel spreadsheet was devised to extract descriptive characteristics and quantitative data (e.g. prevalence rates) from all the eligible studies. The first and second authors each independently carried out the searches, study selection and data extraction (kappa co-efficient = 0.83).

2.4. Risk of bias assessment

The risk of bias was evaluated using an adapted form of the Newcastle Ottawa cohort scale for cross-sectional and cohort studies [20]. This scale assessed the following areas:

- Sample representativeness: one star awarded where the patient sample was representative of the primary care population in the country of origin.
- Sample size: at least 100 was awarded one star; zero stars were awarded for a sample size below this value.
- Response rate: at least 70% was deemed satisfactory; a rate lower than this or not reported received zero stars.
- Ascertainment of the exposure: where a validated measurement tool

was used, two stars were awarded. One star was awarded if a non-validated measurement tool was used but adequately described.
- Control of confounding variables: a maximum of two stars awarded.
- Assessment of outcome: two stars awarded where independent blind assessment or record linkage was involved; one star where the assessment involved self-reporting.
- Appropriate statistical analysis: one star awarded if a clearly described and appropriate statistical test was used to analyze the data.

This provided an overall star-based score ranging from 0 (lowest grade) to 10 (highest grade). Studies which scored 7 or more stars were considered low risk.

2.5. Analyses

Our primary outcome was the percentage of primary care patients with diagnosed depression who have unrecognized bipolar disorder. Data were pooled using the metaprop command [21] in Stata 15. As proportions were often expected to be small, we used Freeman-Tukey Double Arcsine transformation [22] to stabilize the variances and then performed a random-effects meta-analysis implementing the DerSimonian-Lairdmethod [23]. Heterogeneity was assessed using the I^2 statistic. Conventionally, I^2 values of 25%, 50%, and 75% indicate low, moderate and high heterogeneity [24]. One sensitivity analysis was conducted to examine whether the main results were affected by the critical appraisal score of the studies. One subgroup analysis was conducted to examine the impact of the screening tool used for bipolar disorder (diagnostic interview or self-report questionnaire) in the prevalence rates of unrecognized bipolar disorder. The Cohen's Q test of between group variance was used to test the significance of the subgroup analysis. All analyses were conducted using a random effects model as we expected significant heterogeneity across the studies [25,26]. Funnel plots were constructed using the metafunnel command [27], and the Egger test was computed using the metabias command to assess small study bias (an indicator of possible publication bias) [28–30].

3. Results

Fig. 1 presents the study selection process. 1122 total citations were initially retrieved. Following the removal of duplicates and the title/abstract and full-text screening, 10 studies met the inclusion criteria [2,11,13,31–37].

3.1. Descriptive characteristics of included studies

The key descriptive characteristics of the 10 studies which examined the prevalence of unrecognized bipolar are presented in Table 1. The total sum of participants was 3803 (sample size ranged from 93 to 1304). Approximately 68% of the sample consisted of women with a mean age of 44 years. Three studies were conducted in the US, three in the UK, one in Canada, one in China, one in Finland and one in Italy. Four studies solely used questionnaire measures to screen for bipolar disorder whereas six studies used clinical interviews (with or without additional questionnaires). All studies were cross-sectional except one longitudinal study.

3.2. Risk of bias results

Studies scored from 6 to 8 stars; 8 studies [2,11,13,31,32,34,35,37] were considered low-risk as they achieved either 7 or 8 stars whereas two studies, Kwong et al. [33] and Sasdelli et al. [36] were considered high-risk because they achieved 6 stars (see eTable 3 in the appendix). Low-risk studies typically used clinical interviews (supplemented by validated questionnaires) to assess the study outcomes and were based on medium to large samples. High-risk studies used self-reported
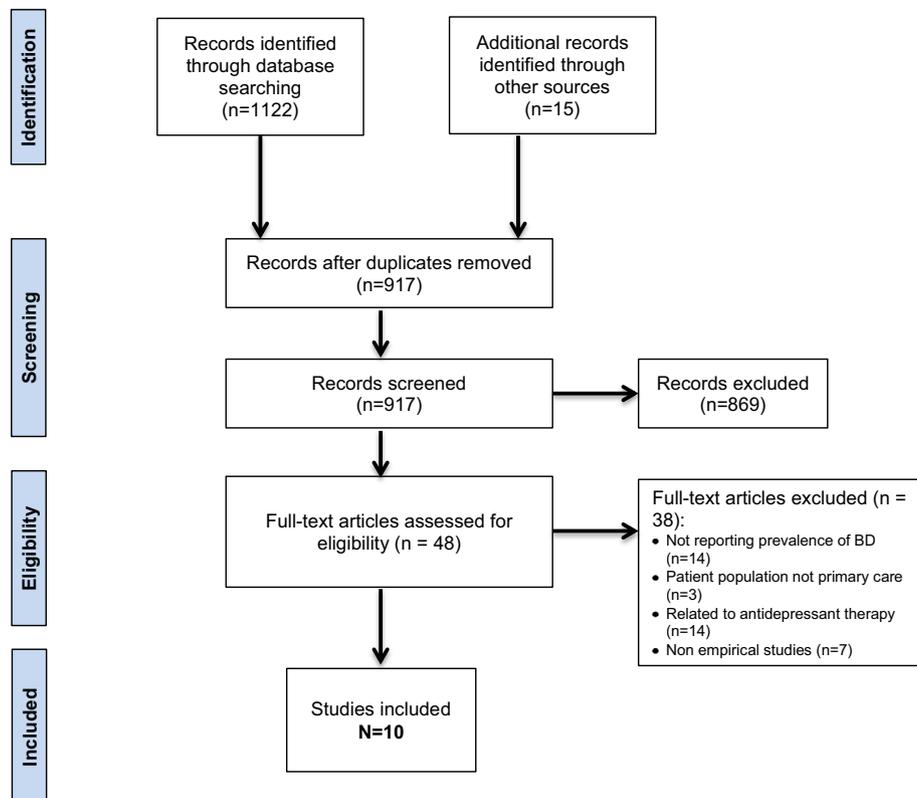
Fig. 1. Flowchart of the study selection process.

questionnaires with possible information bias and were based on small samples.

3.3. Prevalence of unrecognized bipolar disorder

The pooled prevalence of bipolar disorder in primary care patients with depression was 17% (95% CI = 12 to 22; Fig. 2) suggesting that 17 out of 100 patients with depression have unrecognized bipolar disorder. However, there were large variations across the studies as indicated by the high degree of heterogeneity (I^2 = 95%, 95% CI = 69% to 100%). The symmetrical funnel plot and the non-significant Egger test (regression coefficient = − 2.37, 95% CI = -4.94. to 0.20, p = 0.07; Fig. 3) indicated no publication bias.

3.4. Sensitivity and subgroup analyses

The sensitivity analysis revealed that the pooled prevalence of bipolar disorder across the low risk studies was similar to the pooled prevalence obtained in the main analysis (17%, 95% OR = 11 to 23; eFigure 1 in the appendix).

The subgroup analysis revealed that the pooled prevalence of bipolar disorder was lower across studies using clinical interviews for assessing the presence of bipolar disorder than studies using self-report questionnaires (14%, 95% CI = 8 to 20 versus 22%, 95% CI = 16 to 28; eFigure 2 in the appendix) but this difference was not statistically significant (Q = 1.27; p = 0.121).

4. Discussion

4.1. Summary

On average, 5–10% of people from the general population are diagnosed with depression every year [38] and we found that 17% of primary care patients diagnosed with depression could have
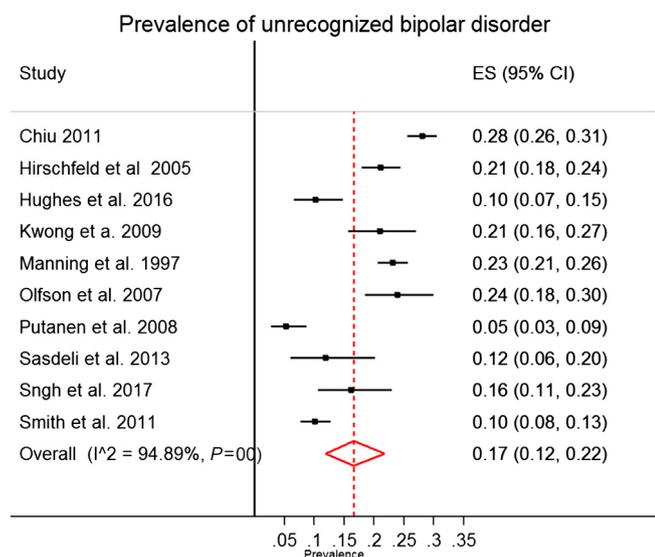
unrecognized bipolar disorder.

4.2. Strengths and limitations

This systematic review has focused on a major issue which concerns a large proportion of patients treated in primary care but surprisingly has received spare attention in research, policy and practice to date. However, there are important limitations. First, the variation across studies was high. Bipolar disorder is classified along a spectrum and most of the identified studies failed to differentiate between the different subtypes of bipolar disorder. Taking into account the benefits and limitations of meta-analysis [39,40], we reported pooled estimates of our outcome. We further accounted for the large heterogeneity by applying random effects models in pooling the prevalence rates of bipolar disorder, by undertaking one subgroup analysis and one sensitivity analysis. Second, the estimates of bipolar disorder misdiagnosis are likely to be conservative in some studies because they are based on the assumption that all those who were eligible for the study but were not interviewed for bipolar disorder did not have bipolar disorder [2,11] whereas the complexity of the sample (diagnosed with combinations of mood disorders and substance use disorders) might account for the high prevalence rate of bipolar disorder misdiagnosis in other studies. Prevalence rates may be over-estimated in certain studies due to the use of self-report questionnaires only (such as the MDQ) rather than diagnostic interviews and also because some studies selected samples which were more likely to have bipolar symptoms. Differences in the sensitivity and specificity of the diagnostic instruments used across the studies should be noted and these may differ across subtypes [31,41]. Third, we excluded grey literature as we considered it would be highly unlikely that large high quality studies on misdiagnosis of bipolar disorder in primary care patients with depression would not be published in peer-reviewed journals [42]. It is reassuring that our formal tests indicated no risk for small study bias.

Table 1
Characteristics of studies examining the prevalence of unrecognized bipolar disorder.

Study	Country	Research design	Assessment of bipolar disorder	Characteristics of participants	Key results	Risk of bias
Chiu [31] 2011	Canada	Cross-sectional study.	Use of the Mood Disorders Questionnaire (MDQ) to identify patients with bipolar disorder symptoms.	1304 adults (mean age = 42.5; male = 41%) surveyed out of 1416 initially contacted from 54 primary care practices, presenting with depression, anxiety, substance use disorders or ADHD; response rate 92%.	**27.9%** of participants screened positive for bipolar disorder symptoms.	7 stars
Hirschfeld et al. [32] 2005	US	Cross-sectional study.	Mood Disorder Questionnaire (MDQ) used followed up by Structured Clinical Interview based on the DSM-IV (SCID).	646 consecutive patients (mean age = 50.1; male = 18%) receiving antidepressants, one urban, academic clinic; response rate not reported.	**21.3%** were screened positive for bipolar disorder using the MDQ. 32.8% using SCID (Note – Not administered randomly).	7 stars
Hughes et al. [2] 2016	UK	Cross-sectional study.	Mood Disorder Questionnaire (MDQ) used followed up by semi-structured standardized diagnostic interviews including consensus meetings with 2 experienced clinicians.	236 responders (mean age = 32.7; male = 22%) out of 2341 patients contacted (all diagnosed with depression only) from 21 general practices in West Yorkshire area i.e. a response rate of 10.1%.	**10%** after adjusting for differences between the sample and data obtained from The Health Improvement Network (THIN) national database provided a more representative sample.	8 stars
Kwong et al. [33] 2009	China	Cross-sectional study.	Using the Mood Disorder Questionnaire (MDQ) amongst patients with depression diagnosed by primary care physicians.	215 consecutive patients (aged 18–65 years, no mean age reported; male = 33%) with past or current diagnosis of depression; response rate not reported.	**20.9%** (MDQ ≥ 7 with 2 or more concurrent symptoms resulting in moderate or severe impairment).	6 stars
Manning et al. [37] 2010	US	Prospective cohort study.	A semi-structured interview similar to the Structured Clinical Interview for DSM-III-R administered by an experienced primary care physician with enhanced training on mood disorders.	108 consecutive non-referred patients (mean age = 33.6; male = 20%) presenting with impairment due to depression or anxiety at a private ambulatory family practice center; response rate not reported.	**23.1%** of patients were diagnosed with bipolar I, II, or III disorder or cyclothymia.	7 stars
Olfson et al. [13] 2005	US	Cross-sectional study.	Using the Mood Disorder Questionnaire (MDQ) amongst patients with depression diagnosed by primary care physicians.	226 random waiting room patients (75% over 45 years; male = 19%) diagnosed with major depression in one urban, academic clinic; response rate 85.9%.	**23.5%** (MDQ ≥ 7 with 2 or more concurrent Symptoms resulting in moderate or severe impairment).	7 stars
Poutanen et al. [34] 2008	Finland	Retrospective cross-sectional study.	ICD-10 main criteria (high mood or irritability) for hypomania, mania or psychotic mania in telephone interview with 3 psychiatrists.	250 responders (mean age = 52.2; male = 51%) in the follow-up out of 430 eligible patients the survey i.e. response rate of 58.1%.	**4.8%** of the primary care patients with clinical depression (mild or severe) had lifetime mood elevation.	8 stars
Sasdelli [36] 2013	Italy	Cross-sectional study.	Mood Disorder Questionnaire (MDQ) and Hypomania Checklist (HCL-32).	93 participants (mean age = 49.1; male = 28%); response rate 99%.	**11.7%** met criteria for Bipolar Disorder II.	6 stars
Singh [35] 2017	UK	Cross-sectional study.	Structured Clinical Interview for DMS-IV (SCID-I), Hypomania Checklist (HCL-13) and brief 3-item questionnaire.	149 participants (mean age = 47; male = 38%); response rate 8.23%.	**16.1%** satisfied criteria for bipolar disorder.	7 stars
Smith et al. [11] 2011	UK	Cross-sectional study.	Hypomania Checklist (HCL-32) and Bipolar Spectrum Diagnostic Scale (BSDS) questionnaires used followed by diagnostic interview/clinical assessment.	576 responders (mean age = 42.8; male = 31%) out of 3117 patients contacted from 11 general practices in the South Wales area i.e. a response rate of 18.5%.	**9.6%** although 2 other estimates calculated: 3.3% (assuming all those who dropped out either at questionnaire or interview did not have bipolar disorder) and 21.6%.	8 stars

Prevalence of unrecognized bipolar disorder

Study		ES (95% CI)
Chiu 2011		0.28 (0.26, 0.31)
Hirschfeld et al 2005		0.21 (0.18, 0.24)
Hughes et al. 2016		0.10 (0.07, 0.15)
Kwong et a. 2009		0.21 (0.16, 0.27)
Manning et al. 1997		0.23 (0.21, 0.26)
Olfson et al. 2007		0.24 (0.18, 0.30)
Putanen et al. 2008		0.05 (0.03, 0.09)
Sasdeli et al. 2013		0.12 (0.06, 0.20)
Sngh et al. 2017		0.16 (0.11, 0.23)
Smith et al. 2011		0.10 (0.08, 0.13)
Overall (I^2 = 94.89%, P=00)		0.17 (0.12, 0.22)

.05 .1 .15 .2 .25 .3 .35
Prevalence

Fig. 2. Forest plot of the prevalence of in primary care patients with depression. Legend: Meta-analysis of individual study and pooled effects. Each line represents one study in the meta-analysis, plotted according to the prevalence of bipolar. The black box on each line shows the prevalence estimate for each study and the red box represents the pooled prevalence rate of bipolar. Random effects model used. 95% CI = 95% confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
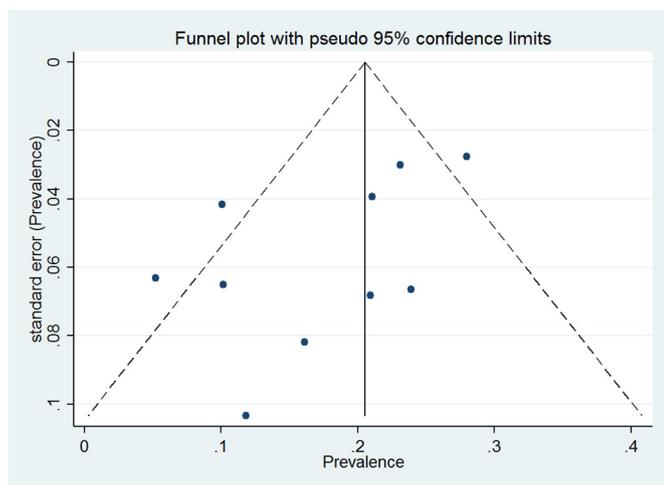
Fig. 3. Funnel plot of prevalence estimates versus standard error for prevalence estimates.
Legend: Funnel plot with pseudo 95% confidence intervals. The outer lines indicate the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity. ES = prevalence estimates; SE = Standard error.

4.3. Comparisons with existing literature

We identified one relevant but more general systematic review published in 2013 which examined the prevalence of unrecognized bipolar disorder across a range of conditions including mood disorders and psychosomatic problems [43]. In our review, we undertook an exhaustive but focused selection approach which allowed us to identify all the relevant studies on bipolar disorder misdiagnosis amongst depressed primary care patients. We report higher prevalence estimates of unrecognized bipolar disorder compared to this previous review. However, we pooled data from 10 studies whereas the previous review descriptively summarized their findings. We also undertook a formal

meta-analysis on the prevalence of unrecognized bipolar disorder.

4.4. Implications for research and practice

Our headline finding is that unrecognized bipolar disorder and the consequent adverse impact of antidepressant monotherapy in primary care patients with depression is a major but overlooked research area. Our figures on the prevalence of unrecognized bipolar disorder are high but not definitive because of the small number of studies that have been conducted globally in primary care settings. Larger prospective studies are required which could also involve younger adults and adolescents, given 50% of bipolar disorder onsets occur by age 25 and 25% occur by age 17 according to the National Comorbidity Survey Replication (NCS-R) [44]. There is also an imperative need to improve the recognition of bipolar disorder in patients treated for depression in primary care, including distinguishing between its subtypes. A lack of effective training of primary care physicians, competing clinical demands and reduced financial incentives combined with mania often being stigmatized and presenting atypically are key reasons for the unrecognition of mental health conditions in primary care [45–47].

In conclusion, our review found that 17% of patients treated for depression in primary care have unrecognized bipolar disorder. These patients are often placed on antidepressant monotherapy which is non-optimal according to international clinical guidelines. Preventable patient harm such as increases in the incidence of mania, hypomania and suicide risk are possible complications [15–17] and improved assessment strategies for bipolar disorder, including its subtypes, in patients presenting with depressive symptoms in primary care are warranted.

Author contributions

The original idea for the research was developed by JD, and AE. The analysis was conducted by JD and MP with input from AE. JD and MP conducted the searches, study selection, quality assessments and other data extraction. JD, MP and AE wrote the paper. All authors interpreted the findings and contributed to critical revision of the manuscript. AE is the guarantor. AE affirms that the manuscript is an honest, accurate, and transparent account of the research findings and no important aspects of the study have been omitted.

Conflicts of interests

All authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2019.03.006.

References

[1] Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet387(10027):1561–1572.
[2] Hughes T, Cardno A, West R, et al. Unrecognised bipolar disorder among UK primary care patients prescribed antidepressants: an observational study. Brit J Gen Pract 2016;66(643):E71–7.
[3] Ferrari AJ, Stockings E, Khoo JP, et al. The prevalence and burden of bipolar disorder: findings from the global burden of disease study 2013. Bipolar Disord 2016;18(5):440–50.
[4] Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 2011;68(3):241–51.
[5] Berk M, Dodd S, Berk L, Opie J. Diagnosis and management of patients with bipolar disorder in primary care. Brit J Gen Pract 2005;55(518):662–4.
[6] Wyatt RJ, Henter I. An economic-evaluation of manic-depressive illness 1991. Soc Psychiatry Psychiatr Epidemiol 1995;30(5):213–9.
[7] 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):337–53.
[8] Lucock M, Olive RE, Sinha A, Horner CQ, Hames R. Graduate primary care mental

health workers providing safe and effective client work: What is realistic? Primary Care Mental Health. vol. 2. 2004. p. 57–66.

[9] Olfson M, Blanco C, Marcus SC. Treatment of adult depression in the United States. JAMA Intern Med 2016;176(10):1482–91.

[10] Culpepper L. The diagnosis and treatment of bipolar disorder: Decision-making in primary care. The primary care companion for CNS disorders. vol. 16. 2014. p. 3.

[11] Smith DJ, Griffiths E, Kelly M, Hood K, Craddock N, Simpson SA. Unrecognised bipolar disorder in primary care patients with depression. Br J Psychiatry J Ment Sci 2011;199(1):49–56.

[12] Titmarsh S. The burden of bipolar disorder in the UK. Prog Neurol Psychiatry 2012;16(5):25–6.

[13] Das AK, Olfson M, Gameroff MJ, et al. Screening for bipolar disorder in a primary care practice. JAMA 2005;293(8):956–63.

[14] Gao KM, Kemp DE, Ganocy SJ, et al. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. Bipolar Disord 2008;10(8):907–15.

[15] Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. J Clin Psychiatry 2000;61(10):804–8.

[16] Pacchiarotti I, Valenti M, Colom F, et al. Differential outcome of bipolar patients receiving antidepressant monotherapy versus combination with an antimanic drug. J Affect Disord 2011;129(1–3):321–6.

[17] Viktorin A, Lichtenstein P, Thase ME, et al. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry 2014;171(10):1067–73.

[18] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000;283(15):2008–12.

[19] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.

[20] Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: advantages and limitations of the Newcastle Ottawa scale. World J Meta-Anal 2017;5(4):80–4.

[21] Kontopantelis E, Reeves D. Metaan: random-effects meta-analysis. Stata J 2010;10(3):395–407.

[22] Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950;21(4):607–11.

[23] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.

[24] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj 2003;327(7414):557–60.

[25] Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med 2001;20(6):825–40.

[26] Kontopantelis E, Reeves D. Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: a comparison between DerSimonian-Laird and restricted maximum likelihood. Stat Methods Med Res 2012;21(6):657–9.

[27] Sterne JAC, Harbord RM. Funnel plots in meta-analysis. Stata J. 2004;4(2):127–41.

[28] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629–34.

[29] Harbord RM, Harris RJ, Sterne JAC. Updated tests for small-study effects in meta-

analyses. Stata J. 2009;9(2):197–210.

[30] Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53(11):1119–29.

[31] Chiu JF, Chokka PR. Prevalence of bipolar disorder symptoms in primary care (ProBiD-PC): a Canadian study. Can Fam Physician 2011;57(2):e58–67.

[32] Hirschfeld RMA, Cass AR, Holt DCL, Carlson CA. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract 2005;18(4):233–9.

[33] Kwong M, Mak K, Law B, Sham S. Preliminary report of a study on the prevalence of bipolar disorders among Chinese adult patients seen in Hong Kong's primary care clinics suffering from depressive illness. J Hong Kong College Fam Phys 2009;31:168–75.

[34] Poutanen O, Koivisto AM, Mattila A, Joukamaa M, Salokangas RKR. Predicting lifetime mood elevation in primary care patients and psychiatric patients. Nord J Psychiatry 2008;62(4):263–71.

[35] Singh S, Scouller P, Smith DJ. Evaluation of the 13-item hypomania checklist and a brief 3-item manic features questionnaire in primary care. BJPsych Bull 2017;41(4):187–91.

[36] Sasdelli A, Lia L, ClaudiaNespeca C, ClaudiaBerardi Domenico, Menchetti M. Screening for bipolar disorder symptoms in depressed primary care attenders: comparison between mood disorder questionnaire and hypomania checklist (HCL-32). Psychiatry J 2013;2013.

[37] Manning JS. Tools to improve differential diagnosis of bipolar disorder in primary care. Prim Care Compan J Clin Psychiatry 2010;12(Suppl. 1):17–22.

[38] Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the world health surveys. Lancet. 2007;370(9590):851–8.

[39] Ioannidis JP, Patsopoulos NA, Rothstein HR. Reasons or excuses for avoiding meta-analysis in forest plots. BMJ 2008;336(7658):1413–5.

[40] Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane library data: the dangers of unobserved heterogeneity in meta-analyses. PLoS One 2013;8(7):e69930.

[41] Dubovsky SL, Leonard K, Griswold K, et al. Bipolar disorder is common in depressed primary care patients. Postgrad Med 2011;123(5):129–33.

[42] McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? Lancet 2000;356(9237):1228–31.

[43] Cerimele JM, Chwastiak LA, Dodson S, Katon WJ. The prevalence of bipolar disorder in primary care patients with depression or other psychiatric complaints: a systematic review. Psychosomatics. 2013;54(6):515–24.

[44] Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 2005;62:593–602.

[45] Grace GD, Christensen RC. Recognizing psychologically masked illnesses: the need for collaborative relationships in mental health care. Prim Care Compan J Clin Psychiatry 2007;9(6):433–6.

[46] Goodrich DE, Kilbourne AM, Nord KM, Bauer MS. Mental health collaborative care and its role in primary care settings. Curr Psychiatry Rep 2013;15(8):383.

[47] Katon W, Unutzer J. Collaborative care models for depression: time to move from evidence to practice. Arch Intern Med 2006;166(21):2304–6.