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Systematic review

Migraine headache and bipolar disorder comorbidity: A systematic review of the literature and clinical implications

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HIGHLIGHTS

- High comorbidity rates between bipolar disorder and migraine exist; most notably among women and patients with bipolar II disorder.
- Comorbidity may portend a more serious clinical course as compared with either condition alone.
- Genetic, neurotransmitter and inflammatory mediators may underlie the association.
- Clinicians need to structure treatment approaches to address both conditions concurrently.

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ABSTRACT

Background and aims: Psychiatric disorders, e.g., depression, are often comorbid with, and can complicate the treatment of, patients with migraine headache. Although empirical work has increasingly focused on the association between migraine and bipolar disorder, this topic has received little attention in the pain literature. Bipolar disorder is a chronic and recurrent mood disorder characterized by cyclic occurrence of elevated (i.e., manic or hypomanic) and depressed mood states. Bipolar I disorder is diagnosed when patients present with at least one abnormally and persistently elevated manic episode; bipolar II disorder is characterized by the presence of hypomanic episodes. Bipolar disorder warrants attention as depressive phases of the disorder can prevail and are often misconstrued by the unwary clinician as unipolar depression. However, treatment for bipolar disorder is distinct from that of unipolar depression and use of antidepressants, which are often invoked in migraine prophylaxis as well as the treatment of depression, may precipitate significant mood changes among bipolar disorder patients. A systematic review of the literature addressing the co-occurrence of bipolar disorder and migraine was conducted. The treatment of dually affected patients is also discussed.

Methods: In order to review the literature to date on migraine and bipolar disorder co-occurrence, a comprehensive search of MEDLINE, EMBASE, PubMed, PsycINFO, Web of Science, and CINAHL for clinic-based and epidemiological studies was conducted using terms related to *migraine* and *bipolar disorder*. Studies were selected for review if they included subjects meeting validated diagnostic criteria for bipolar disorder as well as migraine headache and if a quantitative description of prevalence rates of comorbid bipolar disorder and migraine were reported. Weighted means of the prevalence rates were calculated to compare with general epidemiological prevalence trends for migraine and bipolar disorder, respectively.

Results: Eleven studies met inclusion criteria. Although findings were constrained by methodological limitations and several low quality studies, clinic- and epidemiological cross-sectional investigations demonstrated a high rate of comorbidity between bipolar disorder and migraine. The weighted mean prevalence rate for migraine headache among bipolar disorder patients was 30.7%; for bipolar disorder among migraineurs, the weighted mean prevalence rates were 9% and 5.9% in clinic-based and epidemiological studies, respectively. The association between bipolar disorder and migraine was most notable among women and patients with the bipolar II disorder subtype.

Conclusions: High rates of comorbidity exist between migraine and bipolar disorder, exceeding estimated prevalence rates for those conditions in the general population. Comorbidity may portend a more serious clinical course for dually afflicted individuals.

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Implications: Clinicians need to structure treatment approaches to address concurrent migraine and bipolar disorder in dually afflicted individuals. Although further evidence-based investigation is warranted to inform optimal treatment approaches for both conditions concurrently, anticonvulsants (e.g., valproate, lamotrigine and topiramate); atypical antipsychotics (e.g., olanzapine or quetiapine); and calcium channel blockers (e.g., verapamil) may be considered.

Contents

1. Introduction

Migraine is among the most disabling of the primary headache disorders, with an estimated prevalence of 12–13%; women are affected at a threefold greater rate than men [1,10,52,84]. There has long been an interest in the psychiatric comorbidities associated with migraine, ranging from mood, anxiety, and substance use disorders, as these conditions can complicate the presentation and management of migraine patients. Among the mood disorders, the research was predominantly focused on the relationship between migraine and depression; previous reviews have consistently demonstrated high comorbidity rates among patients with, and a bidirectional relationship between, migraine and depression in clinical as well as community settings [5,32,51,86]. Until recently, little attention had been given to the possibility that migraine may be associated with bipolar disorder.

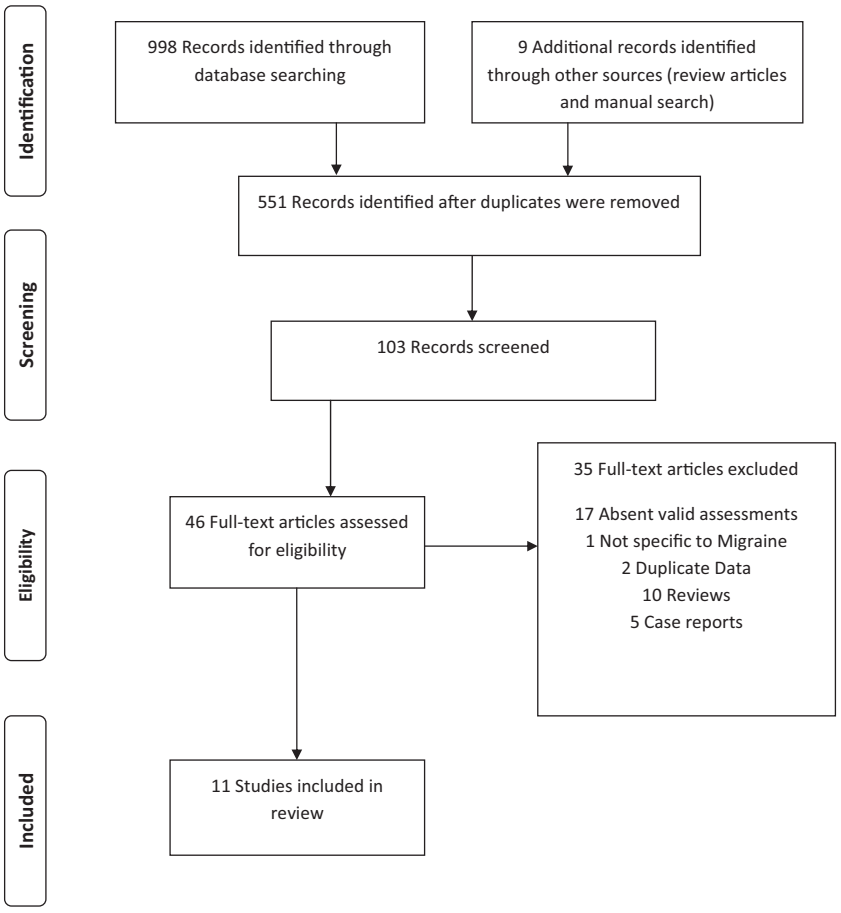
Bipolar disorder is a chronic, recurrent and often severe mood disorder characterized by cyclic occurrence of elevated (manic or hypomanic) and depressed mood states. The illness, which includes bipolar I (defined by the presence of mania) and bipolar II (defined by the presence of hypomania) subtypes [4], exerts a significant toll in terms of quality of life, adaptive functioning, comorbidity and mortality [42]. The lifetime prevalences of bipolar I and II disorders are estimated to be 1% and 1.1% of the general population, respectively [44,61]. In the composite, the 12-month prevalence of bipolar disorder (including bipolar I, II and subthreshold variants) is estimated to affect 2.8% of the general population [61]. Depressive symptoms and episodes can dominate the long-term course of persons with bipolar disorder. For example, it has been estimated that 20–30% of individuals receiving antidepressant therapy for what were thought to be clinically significant depressive symptoms instead had a bipolar disorder subtype [36,55,71]. Given the association between migraine and depression, it is conceivable that clinicians can be misled by depressive symptoms in a migraineur. Yet, failure to correctly diagnose bipolar disorder has serious implications, especially in light of the fact that failure to implement appropriate treatment, i.e., employing antidepressant monotherapy instead of mood stabilizing treatment, can impact morbidity.

A recently published meta-analysis [28] of published articles revealed a pooled migraine prevalence of 34.8% among clinical samples of bipolar disorder patients. The authors did not include studies assessing rates of bipolar disorder among samples of migraine patients; the latter would be of particular relevance to pain practitioners. In this paper, a systematic review of the evidence in the literature to date addressing the co-occurrence of bipolar disorder and migraine was conducted (encompassing epidemiological as well as cross-sectional observational studies assessing patients with migraine). The potential ramifications that such findings have regarding clinical identification and treatment of patients who are dually affected will also be discussed.

2. Methods

2.1. Data sources

The objective was to review the available data related to the co-occurrence of migraine and bipolar disorder including observational studies reporting prevalence rates of migraine among individuals with bipolar disorder as well as those reporting prevalence rates of bipolar disorder among migraineurs. Weighted means of the prevalence rates reported in comorbidity studies were calculated to compare with general epidemiological prevalence trends for migraine and bipolar disorder, respectively. A comprehensive search of MEDLINE (1946-current), EMBASE, PsycINFO (1967-current), PubMed (1977-current) and CINAHL (1946-current), was conducted until July 2015. The search



[a]Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[48] (www.prisma-statement.org)

Fig. 1. PRISMA[a] flow diagram for study selection. [a]Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [48] (www.prisma-statement.org).

strategy was based on title, abstract, and MeSH terms, for *migraine* AND *affective disorders* OR *bipolar disorder* OR *manic depression* OR *mood disorders*. A Web of Science (1994-current) search employing a keyword search of *migraine*$ AND *bipolar disorder*$ was also conducted. The search strategy employed can be found in Fig. 1. Articles generated by the searches were screened by title and abstract review.

Subsequently, full text review of publications was conducted. A manual review of relevant article reference lists was also conducted for eligible studies.

2.2. Study selection

English language publications were considered for inclusion. Studies were selected for the review if they included the following: (1) subjects meeting validated diagnostic criteria for bipolar disorder (e.g., defined according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria [4] or DSM-based standardized interview scales), (2) subjects meeting validated diagnostic criteria for migraine headache (e.g., defined according to International Headache Society (IHS)-based criteria [33,34] or a standardized interview/scale based on IHS-criteria), and (3) a quantitative description of prevalence rates of comorbid bipolar disorder and migraine. If prevalence data for multiple psychiatric disorders were assessed, data pertaining specifically to patients diagnosed with bipolar disorder were extracted for purposes of this review.

2.3. Quality assessment

Quality assessment of included studies was based upon rating of the following criteria (adapted from criteria employed in similar research examining bipolar comorbidity among migraineurs [27,28]): (a) representativeness of the sample employed (0–1 points); (b) a priori design focused on the comorbidity of migraine and bipolar disorder (0–2 points); (c) longitudinal follow-up for 1 year or greater (0–2 points); (d) use of valid diagnostic criteria (0–2 points); (e) control of potential confounding variables (0–2 points); (f) reliability of methods employed to gather clinical diagnostic data upon which diagnostic classifications are based (0–2 points); (g) use of diagnostic criteria to accurately classify between subtypes of bipolar and/or migraine (0–2 points); and (h) appropriateness of the sample size (0–2 points). The maximal possible rating score was 15. Study quality was classified according to the following rating score ranges: high quality, 11–15; intermediate quality, 6–10; and low quality, 0–5.

2.4. Data extraction

The authors independently examined the studies to determine inclusion eligibility and quality assessment; conflicts were resolved by discussion. Because this study consisted of a review of published, publicly available research data, Institutional Review Board approval was not required.

3. Results

As illustrated in Fig. 1, the initial database search yielded 551 articles after duplicates were removed (MEDLINE = 99, EMBASE = 106, PsycINFO = 120, PubMed = 123, Web of Science = 94, CINAHL = 0, other = 9). Of these, 103 had titles and/or abstracts suggesting they might be eligible for inclusion; the remaining articles were deemed to be unrelated, e.g., failing to address comorbidity of bipolar disorder and migraine, or focused on neurologic, biological, genetic or pharmacologic facets of migraine or bipolar disorder, etc. From this pool, 46 articles were examined by the two authors as they specifically addressed comorbidity of migraine and bipolar disorder. Articles were excluded for several reasons. Reports examining the prevalence of non-specific headache but which did not assess for migraine specifically [20], that focused on the impact of migraine on major depressive episodes among mood disordered patients [38], or that did not involve some form of direct case assessment, i.e., inferring comorbidity indirectly from prescription trend data [68] or diagnostic labels obtained from data bases [21,37,40], such as Medicaid claims data, were excluded from this review. Studies failing to employ standardized assessments for participant inclusion, e.g., self-reported history of physician diagnosis of migraine, were also excluded [12,18,22,30,41,56,58,65,66,75,77,87]. Reports presenting duplicate data from previously published investigations were included only once in this review [14,16]. Lastly, qualitative reviews [5,14,16,17,27,28,31,32,43,51,58,79] and case reports [23,39,54,72,88] were excluded.

3.1. Sample characteristics

Eleven articles met inclusion criteria. Sample characteristics, assessments and general findings for the 11 studies are summarized in Table 1. Characteristics of sampled index cases were demographically and clinically heterogeneous. Eight studies employed participants derived from clinical settings whereas three consisted of epidemiological studies. Clinically derived samples also varied considerably, e.g., ranging in bipolar disorder severity from those hospitalized in psychiatric units to outpatients. Samples of participants with migraine ranged from those attending specialized clinics to those with uncertain severity and/or treatment status, i.e., derived from representative samples of health maintenance organization (HMO) members or the general population. Six studies included a comparator group, e.g., a comparison sample of persons with unipolar affective disorder, non-migraine headache, or matched healthy participants from a normative population sample [7,15,24,62,67,78].

The extracted studies were ranked for quality as follows: "low" ($n = 4$, mean total score = 4.3); "intermediate" ($n = 5$, mean total score = 8.4); and "high" quality ($n = 2$, mean total score = 11.5). Quality assessments are summarized in Table 1.

Because of the aforementioned methodological differences, we conducted a narrative descriptive review instead of a quantitative meta-analysis. The findings are summarized below.

3.2. Prevalence rates of migraine among bipolar disorder patients

Seven reports were reviewed (see Table 2), encompassing 783[1] patients with bipolar disorder [7,24,25,50,53,67,73]. Samples were derived from inpatient and/or outpatient clinic settings [24,25,50,67] or enlisted participants from patient registries [7,53,73]. Migraine diagnosis was established using IHS-based criteria in six studies [24,25,50,53,67,73]; a validated scale compatible with IHS criteria formed the basis of headache diagnosis in another [7]. Diagnostic criteria for the presence of bipolar disorder were based upon the version of the DSM available at the time of the study.

The prevalence estimates of migraine among bipolar disorder index cases ranged from 15.7% to 58%; the weighted mean prevalence rate was 30.4% [7,24,25,50,53,67,73]. Seldom were rates of migraine among bipolar disorder patients compared with other patients or controls. Bipolar disorder was second only to major depressive disorder in terms of prevalence of migraine among patients assessed in psychiatric clinical settings, but was more common than other psychiatric disorders, e.g., anxiety disorders [7,24,25,67]. A higher, but not statistically significant, rate of migraine was observed among bipolar disorder patients as compared to a sample derived from the general population in another study [7].

Six studies distinguished between patients with bipolar I and bipolar II disorders [7,24,25,50,67,73]. Prevalence estimates of migraine among bipolar I patients ranged from 14% to 28.6%. For bipolar II patients, the range was considerably wider, i.e., 6.3–82.1%, likely due to differences across studies in the criteria employed to assess bipolar II disorder [24,25,67]. The weighted mean prevalence rates of migraine among participants with bipolar I and bipolar II disorder were 21.1% and 41.7%, respectively [7,24,25,50,67,73]. Statistical comparison revealed significantly higher rates of migraine among patients with bipolar II disorder as compared to those with bipolar I disorder in one study [73] and another revealed that the proportion of bipolar II patients with migraine was significantly greater than bipolar II patients without migraine [25]. Interestingly, one study revealed the reverse trend, i.e., that migraine was more common among bipolar I disorder than among bipolar II disorder patients [7].

Three studies observed that migraine was more common among women, as compared with men, diagnosed with bipolar disorder [7,24,50]. However, there were some inconsistencies in the studies reviewed here. One study demonstrated almost equal proportions of migraine among men and women with bipolar disorder [53] and another, failed to demonstrate any significant gender differences among afflicted patients [73]. The remaining studies did not examine or report gender differences [25,67].

3.3. Prevalence rates of bipolar disorder among index cases with migraine

The observed prevalence rates of bipolar disorder among index migraine cases are summarized in Table 3. Two clinic-based cross sectional studies encompassing 1102 migraine patients were acquired [73,76]. IHS-based criteria formed the basis for identifying index migraine cases. Diagnosis of bipolar disorder was based upon DSM criteria available at the time of the study [73,76]. The weighted mean prevalence rate of bipolar disorder among clinic participants with migraine was 9% [73,76]; 3.2-fold greater than the 12-month prevalence rates of bipolar disorder variants in the general population. Rates of comorbid bipolar II disorder were reportedly higher than those for bipolar I disorder among migraine clinic patients; the weighted mean prevalence rates were 2.9% and 2.4%, respectively [73,76]. None of the studies assessed gender differences in the prevalence rates of bipolar disorder among migraineurs [73,76].

Three epidemiological studies encompassing 6948 participants were acquired [15,62,78]. IHS-based criteria formed the basis for identifying index migraine cases. Diagnosis of bipolar disorder was based upon DSM criteria available at the time of the study [15,62] or the World Health Organization – Composite International Diagnostic Interview [78]. Each of the epidemiological studies reported statistically significant odds ratios for the comorbidity of bipolar

[1] Fifty patients included in the Fasmer and Oedegaard (2001) [25] paper were subsequently included in a larger study by Oedegaard et al. (2005) [67].

Table 1
Sample characteristics and assessments of included studies.

Study (country)	Design	Sample	Methods	Outcome variable	Results	Quality score/rating
Studies which indexed cases based on psychiatric diagnosis						
Mahmood et al. (1999) [53] (New Zealand)	Cross sectional	81 bipolar patients derived from a patient registry; mean age = 42.6 years (range 20–70 years); 44 men; 37 women	Patients surveyed for migraine	Prevalence of migraine	High rates of migraine are encountered among bipolar patients; migraineurs had an earlier onset of bipolar illness and greater psychosocial impairment as compared with those without migraine	(a) 0 (b) 2 (c) 0 (d) 1 (e) 0 (f) 1 (g) 0 (h) 0 Total: 4 Rating: low
Fasmer (2001) [24] (Norway)	Cross sectional	62 consecutively admitted psychiatric inpatients with affective disorders of whom 27 were diagnosed with bipolar disorder (22 women; 5 men); mean age = 37 years (range 20–57 years)	Patients surveyed for lifetime migraine, as well as migraine over the last year and the last month	Prevalence of migraine	Migraine was commonly encountered in unipolar and bipolar patients (no significant differences); migraine was significantly more frequent among bipolar II than bipolar I patients	(a) 0 (b) 2 (c) 0 (d) 1 (e) 0 (f) 0 (g) 1 (h) 0 Total: 4 Rating: low
Fasmer and Oedegaard (2001) [25] (Norway)	Cross sectional	81 consecutively admitted psychiatric inpatients and 21 outpatients (total n = 102) with affective disorders of whom 50 were diagnosed with bipolar disorder (69% women;31% men); mean age = 38.5 years (range 18–65 years)	Patients surveyed for lifetime migraine, and migraine over last year and last month	Prevalence of migraine and characteristics of affective disorders in patients with comorbid migraine subtypes	Migraine was commonly encountered in unipolar and bipolar patients (no significant differences); among migraineurs, most had bipolar II and individuals without migraine were more likely to have bipolar I	(a) 0 (b) 2 (c) 0 (d) 1 (e) 0 (f) 0 (g) 1 (h) 0 Total: 4 Rating: low
Low et al. (2003) [50] (Canada)	Cross sectional	108 bipolar disorder outpatients (73 women; 35 men); mean age = 44.8 ± 13.25 years	Questionnaire to assess lifetime prevalence of migraine	Prevalence of migraine	Migraine was common among bipolar patients; women > men; co-afflicted patients were more apt to present with depression symptoms than mania or hypomania and required fewer hospitalizations than those without migraine	(a) 1 (b) 2 (c) 0 (d) 2 (e) 2 (f) 0 (g) 2 (h) 1 Total: 10 Rating: intermed
Oedegaard et al. (2005) [67] (Norway)	Cross sectional	201 psychiatric patients (177 inpatients; 24 outpatients) of whom 87 were diagnosed with bipolar disorder; mean age = 36.9 ± 10.2 years	Patients surveyed for migraine with and without aura as well as migraine aura without headache, along with the frequency of attacks	Prevalence of, and characteristics of, the affective disorders in patients with comorbid migraine subtypes	Migraine with aura was more common than migraine aura without headache across all affective disorders; those with migraine with aura had a later age of onset of headache and less suicidality	(a) 1 (b) 0 (c) 0 (d) 1 (e) 1 (f) 0 (g) 2 (h) 1 Total: 6 Rating: intermed
Ortiz et al. (2010) [73] (Canada)	Cross sectional	323 participants with bipolar disorders derived from two patient registries (61.6% women; 38.4% men); 204 had BP I, 92 had BP II and 27 had BP NOS; mean ages for two samples were 51.5 ± 11.9 and 46.4 ± 13.5 years	Patients surveyed for migraine	Prevalence of migraine and characteristics of bipolar patients with and without migraine	Migraine was significantly more common among bipolar II as compared with Bipolar I patients; migraine without aura was most common. Co-afflicted patients had higher rates of suicide and anxiety disorders	(a) 1 (b) 3 (c) 0 (d) 1 (e) 2 (f) 1 (g) 2 (h) 2 Total: 12 Rating: high
Baptista et al. (2012) [7] (Venezuela)	Cross Sectional	1059 psychiatric inpatients and outpatients of whom 157 were diagnosed with bipolar disorder (BP), 445 first-degree relatives, and 516 controls (C) from general population. Mean ages = 38.9 ± 15.1 years for (C), 43.2 ± 14.4 years for (BP)	Participants surveyed for migraine	Comparison of prevalence rates of migraine across groups and gender	A higher but not statistically significant rate of migraine was noted among patients with bipolar disorder; women with bipolar disorder had 8 times the rate of migraine than men with bipolar disorder	(a) 1 (b) 2 (c) 0 (d) 2 (e) 2 (f) 0 (g) 2 (h) 1 Total: 10 Rating: intermed

Table 1 (*Continued*)

Study (country)	Design	Sample	Methods	Outcome variable	Results	Quality score/rating
Studies which indexed cases based on migraine diagnosis						
Robbins and Ludmer (2000) [76] (United States)	Cross sectional	1000 consecutive migraine patients seeking treatment in a specialty migraine clinic; age range 30–81 years	Patient interviewed for lifetime history of bipolar disorder	Lifetime prevalence of bipolar disorder subtypes	Bipolar disorder subtypes were relatively common among migraineurs	(a) 0 (b) 1 (c) 0 (d) 1 (e) 0 (f) 1 (g) 1 (h) 2 Total: 6 Rating: intermed
Ortiz et al. (2010) [73] (Canada)	Cross sectional	102 patients from a specialty migraine clinic (77 women; 25 men); mean age = 45.7 ± 11.7 years	Patients surveyed for current and lifetime psychiatric history	Prevalence of psychiatric disorders	Unipolar depression and bipolar II disorder were the most common mood disorders among migraineurs	(a) 1 (b) 3 (c) 0 (d) 1 (e) 2 (f) 1 (g) 2 (h) 1 Total: 11 Rating: high
Merikangas et al. (1990) [62] (Switzerland)	Cohort study	Random sample of 457 persons drawn from the community (232 women; 225 men). Participants were assessed initially and re-interviewed at 8 years. Age range 27–28 years	Participants were interviewed for 1-year prevalence of psychiatric disorders	Prevalence of psychiatric disorders as compared among migraineurs and those without migraine	Migraineurs had significantly higher rates of affective disorders as compared with those without migraine, including bipolar spectrum disorder	(a) 0 (b) 1 (c) 1 (d) 1 (e) 0 (f) 1 (g) 0 (h) 1 Total: 5 Rating: low
Breslau et al. (1991) [15] (United States)	Cohort study	Random sample of 1200 persons drawn from a 400,000 member HMO; 1007 participated initially and 979 were re-interviewed at 3.5 years. Those with migraine (12.8%) were compared with those without. Age range 21–30 years	Participants were interviewed for lifetime psychiatric history	Prevalence of psychiatric disorders as compared among migraineurs with and without aura	Migraineurs had significantly higher rates of affective disorders as compared with those without migraine, including bipolar disorder. Odds ratios of affective disorders associated with migraine with aura were higher than those associated with migraine without aura	(a) 1 (b) 2 (c) 0 (d) 2 (e) 1 (f) 1 (g) 1 (h) 2 Total: 10 Rating: intermed
Saunders et al. (2008) [78] (United States)	Cross sectional	5484 participants from a nationally representative household survey (3153 women; 2331 men). Age range 18+ years	Participants were interviewed for migraine, other headache, comorbid psychiatric and chronic medical conditions	Prevalence of psychiatric disorders, comorbid conditions and degree of disability among persons with migraine, other headache and no headache	Compared with headache-free subjects, headache-afflicted persons were at significantly increased risk for mental disorders, other pain conditions, and physical diseases. Migraineurs experienced greater role disability than persons with nonmigraine headaches and headache-free persons	(a) 1 (b) 2 (c) 0 (d) 1 (e) 2 (f) 2 (g) 1 (h) 2 Total: 11 Rating: high

disorder among migraineurs as compared with non-migraineurs [15,62,78]. Two epidemiologic studies derived samples from the community [62,78] and one derived a random sample from a HMO [15]. Due to concerns about selection bias from being derived from a clinical population, in contrast to community-based samples, the latter study was not included in the calculation of weighted means of co-prevalence of migraine and bipolar. The weighted mean prevalence rate of bipolar disorder among participants with migraine in community-based epidemiological studies was 5.9% [62,78]; 2.1-fold greater than the 12-month prevalence rates of bipolar disorder variants in the general population.

Only one study distinguished between the association between subtypes of bipolar disorder and migraine with aura or without aura, respectively [15]. In the latter investigation, only migraine with aura was found to have a significant relationship with either bipolar disorder subtype.

4. Discussion

An emerging body of research has drawn attention to the psychiatric disorders accompanying migraine. We systematically reviewed existing studies on the comorbidity between bipolar disorder and migraine. Ultimately, 11 cross-sectional studies met the inclusion criteria. The methodological limitations and low quality ratings of several of these studies temper the findings [24,25,53,62]. Several of the prevalence rates reported here were based upon small sample sizes of indexed bipolar or migraine cases [24,25,53,62,73]. In addition, studies varied in design and

Table 2
Prevalence of migraine among participants with bipolar disorder.

Study	IHS-based migraine criteria	Bipolar criteria	No. of bipolar Cases	Prevalence of migraine	Gender subanalysis	Bipolar subanalysis
Mahmood et al. (1999) [53]	Yes	DSM-III-R	81	25.9%	27% women, 25% men; NS	NR
Fasmer (2001) [24]	Yes	DSM-IV	27	45%	48% women, 39% men	14% BD I, 77% BD II; $p < 0.001$;
Fasmer and Oedegaard (2001) [25]	Yes	DSM-IV	50	58%	NR	27.3% BD I, 82.1% BD II; among BD II, migraine > no migraine, $p < 0.001$
Low et al. (2003) [50]	Yes	DSM-IV	108	39.8%	43.8% women, 31.4% men	28.6% BD I; 64.7% BD II
Oedegaard et al. (2005) [67]	Yes	DSM-IV	87	50.6%	NR	25% BD I; 68.6% BD II
Ortiz et al. (2010) [73]	Yes	DSM-IV	323	24.5%	No gender differences	19.2% BD I; 34.8% BD II; $p < 0.005$
Baptista et al. (2012) [7]	Yes[a]	DSM-IV	157	15.7%	23.1% women, 2.9% men; NS	16.7% BD I; 6.3% BD II; 17.1% BD NOS
Weighted means				30.36%		21.05% BD I; 41.7% BD II

Notes: NR = not reported; BD I = bipolar I disorder; BD II = bipolar II disorder; p = p-value; BD NOS = bipolar disorder, not otherwise specified.
[a] Used Lipton's scale which was validated and compatible with IHS-criteria.

Table 3
Prevalence of bipolar disorder among participants with migraine.

Study	IHS-based migraine criteria	Bipolar criteria	No. of migraine cases	Prevalence of bipolar D/O	Other subanalysis
Studies which indexed migraine cases from clinic settings					
Robbins and Ludmer (2000) [76]	Yes	DSM-IV	1000	8.6%	BD I 2.1%; BD II 2.4%; BD NOS 2.8%
Ortiz et al. (2010) [73]	Yes	SADS-L; DSM-IV	102	12.7%	BD I 4.9%; BD II 7.8%
Weighted means				8.97%	2.36% BD I; 2.89% BD II
Study	**IHS-based migraine criteria**	**Bipolar criteria**	**Total *N***	**Prevalence of bipolar D/O**	**Migraine and bipolar D/O OR (95% CI)**
Epidemiological study which indexed cases from a Health Maintenance Organization based on migraine diagnosis					
Breslau et al. (1991) [15]	Yes	DIS, DSM-III-R	1007 (migraine $N = 128$; no migraine $N = 879$)	4.7% BD I 3.9% BD II	Migraine vs. none OR = 4.7 (1.4–15.4) Migraine with aura: BD I 7.3 (2.2–24.6); BD II 5.2 (1.4–19.9) Migraine without aura: BD I 2.4 (0.5–11.3); BD II 2.5 (0.5–11.9)
Study	**IHS-based migraine criteria**	**Bipolar criteria**	**Total *N***	**Prevalence of bipolar D/O**	**Migraine and bipolar D/O OR (95% CI)**
Epidemiological studies which indexed cases from community settings based on migraine diagnosis					
Merikangas et al. (1990) [62]	Modified	DSM-III-R	457 (migraine $N = 61$; no migraine $N = 396$)	8.8%	Migraine vs. none OR = 2.9 (1.1–8.6)
Saunders et al. (2008) [78]	Yes	WHM-CIDI	5484 (migraine $N = 317$; other headache $N = 400$; no headache $N = 4767$)	5.3%	Migraine vs. no headache OR = 3.9 (2.3–6.5)
Weighted means				5.9%	

Notes: BD I = bipolar I disorder; BD II = bipolar II disorder; BD NOS = bipolar disorder, not otherwise specified; SADS = schedule for affective disorders and schizophrenia – lifetime version; OR = odds ratio; 95% CI = 95% confidence interval; DIS = National Institute of Mental Health Diagnostic Interview Scale; HMO = Health-Maintenance Organization; WHM-CIDI = World Mental Health version of the Composite International Diagnostic Interview.

analyses, e.g., sampling differences with regard to age, gender, source of the samples, as well as the types of comparator groups employed. The diagnostic nosology employed for index case identification varied across studies potentially influencing observed prevalence rates. For example, migraine cases varied depending on whether studies used the 1988 or 2004 edition of the International Headache criteria [33,34]; those for bipolar disorder diagnosis, may have varied depending on the version of the DSM employed at the time of the study. Criteria employed for identifying index cases with bipolar II disorder varied across some of the studies as well [24,25,67].

Interpreting the results of clinic-based studies assessing comorbidity is challenging as there is potential for spurious results arising from selection, i.e., Berkson's bias [8]. The latter refers to the propensity of clinical samples to be enriched as related to another pathological condition. Although the propensity to recognize and refer patients for comorbid conditions in clinical samples is influenced by the patterns of diagnosis and referral of treatment

providers in those settings, individuals who are so ill to require treatment may be at a higher risk of having a related comorbid condition than that which prevails in a random sample of the population. The results of population-based cross-sectional studies evaluating comorbidity in unselected populations, although few in number within this review, may offer particular advantages over those derived from clinic-based studies [15,62,78]. However, even in one of these epidemiological studies retrieved here [15], participants were derived from an HMO, and as a result, rates of bipolar disorder obtained may have been unduly influenced by referral patterns of clinicians treating those patients.

4.1. Migraine and bipolar disorder comorbidity

The above limitations notwithstanding, several notable trends emerged. Our findings suggest that approximately one-third of persons diagnosed with bipolar disorder are afflicted with migraine [7,24,25,50,53,67,73]. These results are comparable to those reported in a meta-analysis of pooled cross-sectional clinical studies of bipolar patients [28]. Although there was considerable overlap in the articles retrieved here and in the aforementioned meta-analysis, our criteria for study selection was more conservative. Fornaro and Stubbs (2015) included two studies [22,77] in their meta-analysis that did not adhere strictly to IHS criteria for migraine, and thus, in the present review, were excluded. Yet, despite these differences, both the present paper and that provided by Fornaro and Stubbs (2015), suggest that migraine co-occurs among bipolar disorder patients at a higher prevalence than the 12–13% rate estimated to occur in the general population. It is unsurprising therefore, that migraine is suggested to be the most common neurologic disorder accompanying bipolar disorder [59].

Although fewer in number, the present review included studies addressing the prevalence of bipolar disorder among migraineurs; the latter would resemble the context that patients would be encountered by, and therefore, would have particular relevance to, pain practitioners. Our findings suggest that the lifetime prevalence of reported bipolar disorder among migraineurs in clinic [73,76] as well as epidemiological studies [15,62,78] exceed expected 12-month prevalence rates for bipolar disorder variants in the general population, i.e., greater than 2.8%. As compared with studies relying on clinic samples of migraine patients, the weighted mean prevalence of bipolar disorder among migraineurs obtained from community-based epidemiological studies suggested a more conservative estimate of the association, which may reflect overestimation due to Berkson's bias in clinic samples. Nonetheless, rates of bipolar disorder and its subtypes appear to be higher among migraineurs, whether drawn from community or clinical settings, than those estimated for the general population.

Among bipolar subtypes, migraine comorbidity appeared to be highest among patients with bipolar II disorder [24,25,50,67,73]. With few exceptions, most of the studies reviewed herein were consistent with general population trends as regards to gender-related prevalence rates for migraine. Migraine was more common among women with bipolar disorder [7,24,50]. Nonetheless, several studies still suggested that migraine occurred at high rates among men with bipolar disorder as well [24,50,53]. Because both migraine headache as well as bipolar II disorder occur more commonly among women as compared with men, it is plausible that gender could potentially account for this association. Only one study demonstrated that the association between migraine and bipolar disorder, including the bipolar II subtype, was independent of gender [73]. It has, as yet, to be deciphered in future research whether bipolar II, independent of patient gender, is associated with an increased risk of migraine headache.

4.2. Clinical course of migraine and bipolar disorder comorbidity

Comorbidity may portend a more difficult clinical course for affected patients [18]. It has been suggested that the presence of migraine might define a subgroup of bipolar patients with a more serious mood disorder [24,50,53,73]. Bipolar disorder patients with comorbid migraine, as compared with those who had bipolar disorder alone, tended to have mood disturbances at a younger age [50,53]; greater psychosocial impairment [53]; more frequent depressive episodes [50]; higher rates of suicide [73] as well as higher rates of other comorbid conditions [24,73]. Conversely, none of the studies reviewed here examined the impact of bipolar disorder on the course of migraine specifically.

None of the retrieved studies assessed participants longitudinally to ascertain how migraine patients co-afflicted with bipolar disorder presented. It is impossible to estimate how many subjects initially presenting with what were presumed to be symptoms of unipolar depression were, on subsequent re-assessment, diagnosed with a bipolar disorder. Interestingly, one study revealed that many patients co-afflicted with bipolar disorder and migraine tended to present with depression initially [50]. This observation, in conjunction with the observation that migraine and bipolar co-afflicted patients have frequent depressive episodes [11,50] increases the likelihood that bipolar disorder may go unrecognized, and therefore, untreated [50,68].

4.3. Treatment implications for patients with migraine and comorbid bipolar disorder

The comorbidity of bipolar disorder and migraine has significant treatment implications. Caution is required as many medications commonly employed for migraine prophylaxis, e.g., antidepressants, will need to be used judiciously, if at all, in patients with bipolar disorder as such agents may increase patient vulnerability towards mania, hypomania, and possibly, rapid cycling [35]. Although this needs to be explored further in future research, dually afflicted individuals may be vulnerable to antidepressant-induced mood changes. The rate of antidepressant-induced switch into mania may be more common in migraineurs as compared to those without migraine [50]. However, differences exist among antidepressant classes in this regard. Treatment with serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants, but not selective serotonin reuptake inhibitors, have been found to be associated with changes in the characteristics of bipolar symptoms among migraine patients, especially those with comorbid bipolar I disorder [77]. Clinicians will, therefore, need to be aware of the potential risk of, and closely monitor dually afflicted patients for, precipitating complications from a mood switch when selecting medications for migraine treatment.

On the other hand, it may be possible to select medications to address bipolar disorder and migraine concurrently. Although there is, as yet, no evidence-based empirical work to inform the most effective treatment approaches to implement, some medications have demonstrated utility in successfully managing both disorders. Several anticonvulsants, including valproate, lamotrigine, and topiramate [23,26,43,49,63,68,72]; atypical antipsychotics, e.g., olanzapine [80] or quetiapine [46]; and calcium channel blockers, e.g., verapamil [6,19,47] may be reasonable medications to employ. Monotherapy with anticonvulsants may, however, be unrealistic because of the differences in the efficacy and dosing requirements for bipolar and migraine disorders [68]. Although some anticonvulsants may potentially contribute to depression [64], anticonvulsants may, when combined with antidepressant prophylactic treatment, reduce the likelihood of inducing mood changes in migraineurs with comorbid bipolar disorder [13,82].

4.4. Pathophysiology underlying migraine and bipolar disorder comorbidity

The pathophysiologic factors subserving the comorbidity of migraine and bipolar disorder remain speculative. Preliminary data suggests that abnormalities in neurotransmitter systems, i.e., serotonin [9,81], dopamine [2], and glutamine [3] are associated with both conditions. Additionally, genetic factors may influence susceptibility to both conditions. For example, a polymorphism in the serotonin transporter [57] may have a role in both conditions. Others suggested that genes conferring risk for bipolar disorder and migraine phenotypes may be linked [69,70]. Recently, evidence has emerged suggesting that common inflammatory mediators may underlie these two conditions, e.g., aberrations in the activation of cytokine-based inflammatory mechanisms [17,29,45] as well as arachidonic acid metabolism [60,74,83,85]. Although the etiologic link between the two conditions has, as yet, to be unveiled, such efforts may eventually inform more effective and targeted therapeutic strategies for co-afflicted individuals.

4.5. Study limitations and suggestions for future studies

The present review may be limited by the stringent selection criteria employed. Expanding the present review to include studies relying on self-report and non-standardized diagnostic criteria for bipolar disorder and/or migraine may have yielded additional adequate quality studies and altered the results reported here [28]. Yet, it was intended to focus the present review solely on the most rigorous and clinically relevant investigations addressing comorbidity. Additionally, the current evidence base is limited by the heterogeneity of samples examined, the number of studies employing diagnostic criteria for migraine and bipolar disorder and the predominance of clinically based cross-sectional studies. These limitations notwithstanding, evidence is growing for the co-occurrence of bipolar disorder and migraine. Methodologically rigorous and longitudinal investigations are warranted to further clarify the relationship between these conditions. Such endeavours may clarify the extent to which migraine comorbidity and severity varies with bipolar subtype and reciprocally, the extent to which bipolar comorbidity and severity varies with migraine subtype. The role of gender, genetic vulnerability and family history play in moderating the association of these two conditions likewise warrants attention.

5. Conclusions and implications

Our study confirmed that rates of comorbidity between migraine and bipolar disorder exceed estimated prevalence rates for these conditions in the general population. Clinicians will need to be cognizant of, and maintain an index of suspicion for, the possible comorbidity, especially among women and bipolar II disorder patients. Depressive episodes can dominate the long-term course of persons with bipolar disorder, leading to misdiagnosis of depression. Failure to implement appropriate treatment for bipolar disorder, e.g., with antidepressants, can predispose patients towards mania, hypomania and rapid cycling. Future endeavours to identify the pathophysiologic factors underlying, and evidence-based treatment approaches to address, comorbid migraine and bipolar disorder are warranted.

Conflict of interest

No competing financial interests exist for the authors.

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