Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2015: 131: 75–88
All rights reserved
DOI: 10.1111/acps.12325

ACTA PSYCHIATRICA SCANDINAVICA

Meta-analysis

The prevalence of pain in bipolar disorder: a systematic review and large-scale meta-analysis

Stubbs B, Eggermont L, Mitchell AJ, De Hert M, Correll CU, Soundy A, Rosenbaum S, Vancampfort D. The prevalence of pain in bipolar disorder: a systematic review and large-scale meta-analysis.

Objective: To conduct a meta-analysis investigating the prevalence of pain in people with bipolar disorder (BD).
Method: A systematic review and random effects meta-analysis searching major electronic databases from inception till 01/2014 in accordance with the PRISMA statement. We included articles reporting quantitative data on the prevalence of pain in people with BD with or without a healthy control group. Two independent authors conducted searches, extracted data, and completed methodological quality assessment.
Results: Twenty two cross-sectional studies were included, representing 12 375 644 individuals (BD n = 171 352, n controls = 12 204 292). The prevalence of pain in people with BD was 28.9% (95% CI = 16.4–43.4%, BD n = 171 352). The relative risk (RR) of pain in BD compared to controls was 2.14 (95% CI = 1.67–2.75%, n = 12 342 577). The prevalence of migraine was 14.2% (95% CI = 10.6–18.3%, BD n = 127 905), and the RR was 3.30 (95% CI = 2.27–4.80%, n = 6 732 220).About 23.7% (95% CI = 13.1–36.3%, n = 106 214) of people with BD experienced chronic pain. Age, percentage of males, methodological quality, and method of BD classification did not explain the observed heterogeneity.
Conclusion: People with BD experience significantly increased levels of pain (particularly chronic pain and migraine). The assessment and treatment of pain should form an integral part of the management of BD.

B. Stubbs[1], L. Eggermont[2], A. J. Mitchell[3], M. De Hert[4], C. U. Correll[5], A. Soundy[6], S. Rosenbaum[7], D. Vancampfort[8]

[1]Department of Health and Social Care, Greenwich, London, UK, [2]Department of Neuropsychology, VU University, Amsterdam, the Netherlands, [3]Department of Psychiatry, University of Leicester, Leicester, UK, [4]KU Leuven – University of Leuven, Department of Neurosciences, UPC KU Leuven, campus Kortenberg, Kortenberg, Belgium, [5]Department of Psychiatry, Albert Einstein College of Medicine, New York, NY, USA, [6]Department of Physiotherapy, University of Birmingham, Birmingham, UK, [7]The George Institute for Global Health and School of Public Health, University of Sydney, Sydney, NSW, Australia and [8]KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium

Key words: pain; chronic pain; migraine; bipolar disorder; severe mental illness

Brendon Stubbs, Department of Health and Social Care, Greenwich, Gray Building Avery Hill Site, London SE9 3SG, UK. E-mail: b.stubbs@greenwich.ac.uk; brendonstubbs@hotmail.com

Accepted for publication July 10, 2014

Summations

- The pooled prevalence of clinical pain in people with bipolar disorder is approximately 28.9%, while 23.7% and 14.2% are affected by chronic pain and migraines respectively.
- Compared with the general population, people with bipolar disorder are at significantly increased risk of reported clinically relevant pain [Relative Risk (RR) = 2.14] and migraine (RR = 3.30).
- Because pain has a range of deleterious impacts on an individual's health and quality of life and may worsen psychiatric symptoms, we recommend that pain assessment and treatment should form part of the routine care of people with bipolar disorder.

Considerations

- There was inconsistency in the assessment methods used to measure pain across the studies.
- There was considerable heterogeneity in each of the pooled analysis that could not be explained by mean age, percentage of males, method of diagnosing bipolar disorder, and methodological quality of the included studies.
- There was insufficient information to determine the influence of the phase of illness and polarity as well as acuity of bipolar symptoms on the observed results.

Introduction

Pain has a deleterious impact on an individual's health and wellbeing (1), and common painful conditions, such as chronic musculoskeletal disorders, contribute to a significant number of years lived with disability across the globe (2). Chronic pain in particular is associated with greatly reduced quality of life and difficulties with activities of daily living and often has a negative impact on an individual's emotional and mental health (3). A substantial body of the literature suggests that those with chronic pain have higher rates of depressive and anxiety symptoms than those without chronic pain (4–6).

Despite this, the prevalence of chronic pain in persons with severe mental illness (SMI) has received little attention (7, 8). This is surprising as persons with SMI such as schizophrenia and bipolar disorder (BD) have a highly increased risk for a plethora of painful physical illnesses including cardiopulmonary diseases, metabolic diseases, bone disorders, viral infections, and cancer (9–12). In addition, pain in people with SMI is also associated with a worsening of psychiatric symptoms (7). Despite this increased risk of severe comorbid physical illnesses, most persons with SMI do not receive adequate physical healthcare provision and treatment (13–15). Mental health specialists report barriers limiting their ability to treat physical comorbidity and people with SMI are less likely to recognize or monitor co-occurring medical conditions than the general population (16, 17). Additionally, many healthcare professionals fail to take people with SMI seriously when they report physical health problems (18). When compared with those without SMI, persons with SMI appear to have an increased likelihood of experiencing conditions that cause pain while at the same time having a lower likelihood of receiving adequate care to manage it (9, 10).

A recent systematic review established that people with schizophrenia, who have been known to have a higher pain threshold for pain than the general population, have a lower prevalence of pain than people with other psychiatric disorders, particularly compared to those with BD (19). However, to date, no systematic review or meta-analysis of pain in individuals with BD exists, despite the fact this group appears to be particularly more likely to experience chronic pain and less likely to seek medical help (8). In fact, people with BD reported almost four pain complaints at any one time (20). Moreover, people with BD who are treatment adherent report statistically lower levels of pain than their non-treatment adherent counterparts (21). Clearly, a better understanding of the risk and burden of pain is an important step toward improving clinical outcomes for individuals with BD.

Aims of the study

In recognition of the potential for pain to be problematic for people with bipolar disorder (BD), the paper had the following two aims: (i) to establish the prevalence of pain and its moderators in people with BD and (ii) to compare the prevalence of pain in BD with general population controls.

Material and methods

This systematic review was conducted according to the PRISMA statement (22) following a predetermined, but unpublished protocol.

Inclusion and exclusion criteria

Studies were eligible that fulfilled the following criteria: (i) inclusion of participants with BD, diagnosed according to diagnostic criteria [e.g. DSM-IV (23) or ICD 10 (24)], a valid screening measure (e.g. Alcohol Use Disorder and Associated Disabilities Interview Schedule—DSM-IV Version) or through medical record review. When we encountered studies containing groups of mixed participants (e.g. with major depressive disorder), we contacted the authors up to two times over a month period to ascertain the variables of interest in BD subjects. If these data were not available, we excluded the study. (ii) Reporting of the prevalence of pain (of any type) or assessment of pain with a continuous measure with or without comparison to a control group that did not have a mental illness. When a study measured pain with a continuous measure, but did not specify prevalence rates with a cut-off point, we contacted the authors up to two times to obtain this information.

We did not place a language restriction upon our searches. If we came across studies that reported data from the same sample at different time points, we used the most recent data and/or the largest data set. We excluded studies that (i) reported pain as an adverse event of a drug trial (e.g. for headache), (ii) reported the prevalence of BD in a sample of patients who all had pain (no other comorbidities were excluded), or (iii) in which the pain was experimentally induced. When we encountered studies without a control group that assessed pain in a sample with a continuous measure [e.g. SF 36 bodily pain scale (25)], but did

not have a cut-off to determine the prevalence of pain, we excluded the study if the authors did not respond to requests for additional data.

Information sources

Two reviewers (BS, DV) independently conducted searches on Academic Search Premier, MEDLINE, EMBASE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus, and Pubmed. In addition, the reference lists of all eligible articles and recent systematic reviews of the literature were scanned to assess eligibility of additional studies.

Searches

Two independent reviewers (BS, DV) employed the predetermined search strategy using the key words 'bipolar disorder' and 'pain' or 'pain perception' or 'pain management' or 'pain measurement' or 'musculoskeletal pain' or 'pain intensity' or 'chronic pain' or 'neuropathic pain' or 'pain*'.

Study selection

After the removal of duplicates, two independent reviewers (BS, DV) screened the titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full text articles was developed through consensus. Two reviewers (BS, DV) then considered the full texts of these articles, and the final list of included articles was reached through consensus.

Data extraction

Two authors (BS, DV) independently conducted data extraction using a predetermined form. The data collected from each article included the following: study design, geographical location, bipolar sample and control sample characteristics (number, % male, mean age), bipolar diagnosis method, method of pain assessment (including site, severity, and interference of pain where available), and the prevalence of pain in people with BD and controls as defined by the authors.

Methodological quality assessment

Two independent authors (BS, DV) completed methodological quality assessment of included articles using the Newcastle Ottawa Scale (NOS) (26). Due to the anticipated paucity of data, we also included studies without a control group. These studies were considered as case–control studies for the purposes of methodological assessment in accordance with a previous review (27).

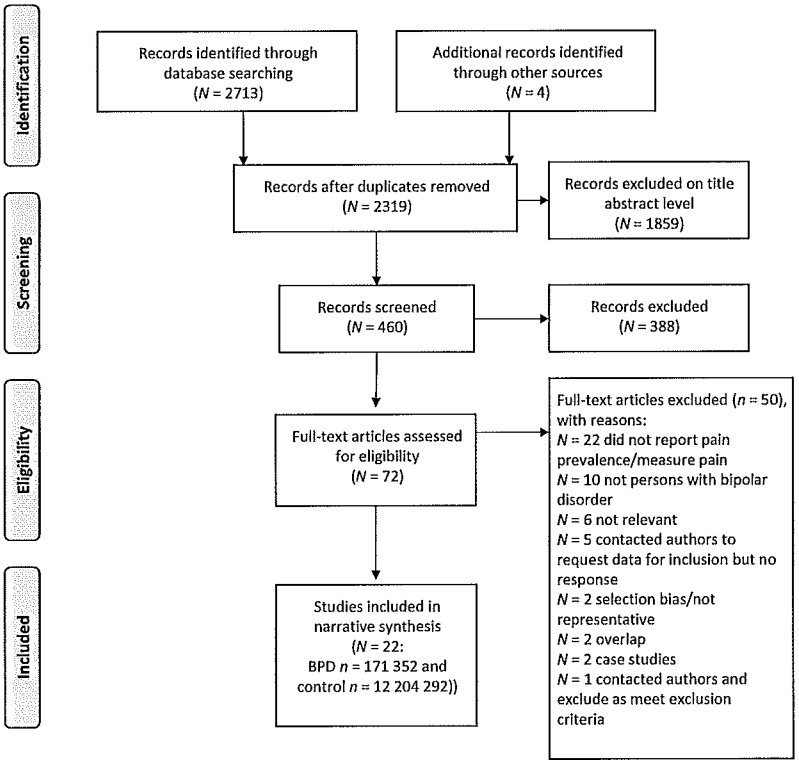

Fig. 1. PRISMA 2009 flow diagram for search strategy.

Table 1. Included study characteristics and methodological quality

Study No	Location and design	Bipolar diagnosis	Participant with BD characteristics	Control participant characteristics	NOS score
8	USA Cross-sectional design collecting data over 1 year	ICD-9-CM Derived from patient electronic medical records	N = 96 186 Age <35 to >80 years Males 81 757 (85.0%) No data on BD severity or medication	N = 4 247 684 Age <35 to >80 years Males 3 882 806 (91.4%)	7
32	Brazil Cross-sectional	DSM IV	N = 339 split in two groups Migraine (n = 115) 41.6 ± 11.20 years Males 16 (17.4%) None migraine (n = 224) 41.5 ± 12.32 years Male 60 (26.7%)	No control group	3
33	USA Cross-sectional study collecting data over 5 year period	ICD-9	N = 3557 39.3 ± 11.8 years Males 1395 (39.2%) BD more likely have substance use disorder OR 2.92; (95% CI, 2.59–3.29%) & alcohol use disorder AOR 19.63; (95% CI, 17.59–21.90%)	N = 726 262 37.7 ± 12.8 years Male 345 146 (47.5%)	7
34	USA Cross-sectional	Composite International Diagnostic Interview Version 3.0	N = 740 39 (±10.6) years Males 414 (56%) No data on BD severity or medication	No control group	3
35	Australia Cross-sectional	DSM IV	N = 67 Males 35.8% (n = 24) 40.4 (±13.5) years BDRS = 11.5 ± 9.3	No control group	3
36	Spain Cross-sectional	DSM-IV-TR	N = 121 50.7 years (±12.3) Males 45 (37.8%) 50.7% had suicidal ideation	No control group	3
37	Italy Cross-sectional	DSM-IV-TR	N = 248 Demographic information not available	No control group	3
38	USA Cross-sectional	AUDADIS-IV	N = 883 36.9 ± 0.3 years Males 380 (43%)	N = 42 210 45.4 ± 0.1 years Males 20 261 (48%)	7
39	UK Cross-sectional retrospective	Not stated	N = 169 Demographic information not available	No control group	3
40	Taiwan Cross-sectional	DSM-IV-TR	N = 10 Demographic data not available	No control group	3
41	USA Cross-sectional retrospective analysis of data over 1 year	ICD-9 medical records	N = 4310 Males 3879 (90%) 53 ± 13 years BD more likely have SUD (P < 0.0001)	N = 3 408 760 Males 3 067 884 (90%) 58 years	8
42	USA Cross-sectional	DSM IV	N = 111 44.8 ± 13.2 years Males 35 (32.4%)	No control group	3
43	Italy Cross-sectional	DSM III	N = 30 Demographic data not available	No control group	3
44	Canada Cross-sectional	CIDI	N = 938 Age 25–64 years Males 436 (46.4%)	N = 32 333 Demographic information not available	7
45	USA Cross-sectional (baseline from RCT)	ICD-9 criteria	N = 384 42.07 ± 11.3 years Males 128 (33.3%)	No control group	3
46	Australia Cross-sectional	ICD 9	N = 27 10 males (37.0%)	No control group	3
47	Canada Cross-sectional	DSM IV	N = 296 with BD 1 and BD 2 49.8 ± 12.7 years % Males not available	No control group	3
48	South Korea Cross-sectional	DSM-IV	N = 190 Demographic data not available	No control group	3

Table 1. (Continued)

Study No	Location and design	Bipolar diagnosis	Participant with BD characteristics	Control participant characteristics	NOS score
49	Scotland Cross-sectional retrospective analysis	GP databases	$N = 2582$ 54.5 years Males 1021 (39.5%)	$N = 1\ 421\ 796$ 47.9 years ($P < 0.001$) Males 698 408 (49.1%)	8
50	Singapore Cross-sectional	CIDI 3.0	$N = 93$ Age 18–65> years Males 47 (50.5%) 66% BD I had severe or moderate manic/hypomanic & 100% respondents with BP-II reported mild clinical severity on the YMRS	Not reported	3
51	United States Cross-sectional	ICD 9	$N = 24206$ All >65 years nursing home residents No specific data on demographics	No control group	3
52	United States Cross-sectional retrospective analysis	ICD 9	$N = 27\ 054$ Demographics not available	$N = 2\ 325\ 247$ Demographics not available	8

BD = bipolar disease; GP = general practitioner; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision; CIDI 3.0 = World Mental Health Composite International Diagnostic Interview version 3.0; AUDADIS-IV = NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version; NOS = Newcastle Ottawa Scale; BDRS = Bipolar Depression Rating Scale; YMRS = Young Mania Rating Scale.

The NOS is utilized to assess the methodological quality of non-randomized trials and has acceptable validity and reliability (26). The assessment tool focuses on three main methodological features: (i) the selection of the groups, (ii) the comparability of the groups, and (iii) the ascertainment of the outcome of interest. The NOS can be modified, and we adapted the NOS to take into account age and gender as comparability measures and considered pain assessment in the exposure category. Studies are given a score from 0 to 9, with a score of 5 or greater being indicative of satisfactory methodological quality. We anticipated studies without a control group would score below this and present their results with due consideration.

Meta-analysis

We pooled individual study data using DerSimonian–Laird proportion method (28). Our predetermined protocol stipulated that heterogeneity would be assessed with the Cochran Q statistic (29). As we found significant heterogeneity [Cochran $Q = 66988.29$ (df = 24), $P < 0.0001$], a random effects meta-analysis was employed using StatsDirect. We calculated the RR to investigate the differences in pain between those with BD and members of the general population when there were three or more studies (Aim ii). When possible, we conducted subgroup analyses to investigate the prevalence of migraine and chronic pain because the literature has suggested that these are prevalent in people with BD (8). In order to investigate sources of heterogeneity, we conducted moderator analysis with mean age, percentage of males, NOS score, and the method of BD classification (comparing DSIM, ICD, or any other screening measure). We assessed publication bias with a visual inspection of funnel plots, yet gave priority to quantitative testing through the Begg–Mazumdar Kendall's tau (30) and Egger bias tests (31).

Results

Study selection

The original search yielded 2713 potential hits which were reduced to 2319 after the removal of duplicates. At the eligibility screening stage, a total of 72 articles were deemed potentially eligible and full texts were obtained and reviewed by two authors. In total, 50 articles were excluded with reasons and 22 articles met the eligibility criteria and were included in the review (8, 32–52). The full search strategy including reasons for exclusion is presented in Fig. 1.

Study characteristics

In total, 171 352 people with BD and 12 204 292 general population controls (total sample size = 12 375 644) were included in the 22 meta-analyzed studies. Details of the included studies are presented in Table 1. All of the studies adopted a cross-sectional measurement of pain, and seven of these (n with BD = 138 285) (8, 33, 38, 41, 44, 49, 52) had a control group without a mental

illness. The sample size of persons with BD across the studies ranged from 10 (40) to 96 186 (8), and the control populations ranged from 32 333 (44) to 4 247 684 (8). The mean age of participants with BD ranged from 39 (34) to over 65 years (51).

Methodological quality

The NOS summary score for each article is presented in Table 1. All seven studies that had a control group scored high (mean NOS score 7.2 ± 0.48) and were considered good quality. The 15 studies that did not have a control group all scored lower than 5 on the NOS, which was attributable to the absence of a control group; these studies scored zero (out of a possible 5 points) in the areas that compare the bipolar and control groups on selection, comparability, and exposure.

Measurement and location of pain in the bipolar populations

A range of different types of pain were considered. The most commonly investigated pain was headache/migraine (8, 32, 33, 35, 39, 40, 42–44, 47, 52) while six studies investigated chronic pain (8, 34, 45, 48–50). A wide range of methods were employed to ascertain pain in people with BD and are presented in Table 2.

Prevalence of pain in persons with bipolar disease

In total, 25 types of pain were investigated, and the pooled prevalence of pain was 28.9% [95% CI: 16.4–43.4%, n = 171 352, Cochran Q = 66988.29 (df = 24), $P < 0.0001$, Fig. 2a]. The funnel plot was asymmetrical (Fig. 2b); however, both the Begg–Mazumdar (Kendall's $\tau = -0.013$; P = 0.908) and Egger bias (Kendall's $\tau = 11.51$; P = 0.4897) tests did not demonstrate any evidence of publication bias. Next, we pooled the prevalence of pain using only one pain measurement from each of the 22 studies, thus including only the highest prevalence of pain from three studies that contained data on pain at two sites (33, 35, 43). The prevalence of clinical pain across 22 studies was 28.4% [95% CI = 15.0–44.1%, Cochran Q = 66477.17 (df = 21), $P < 0.0001$]. Within this analysis, there was also no evidence of publication bias (Egger: bias = 12.44, P = 0.5176, Begg–Mazumdar: Kendall's $\tau = 0.021$, P = 0.9113).

Moderators of the prevalence of pain in people with BD

Ten studies (32–36, 38, 41, 42, 45, 49) had sufficient data on mean age, percentage of males, and bipolar diagnosis method to enable moderator analyses. The moderator analyses demonstrated that mean age ($b1 = -0.038$, $z = -0.311$, P = 0.75), % male ($b2 = -0.074$, $z = -1.013$, P = 0.311), and method of diagnosing BD ($b3 = -0.0935$, $z = -0.092$, P = 0.92) did not explain the heterogeneity in the prevalence of pain. We investigated the effect of methodological quality (NOS score) on the prevalence of pain across the 22 studies, and this suggested that a low NOS score was associated with a high prevalence of pain but this did not reach statistical significance ($b1 = 0.532$, $z = 1.875$, P = 0.06). Lastly, we investigated the influence of the method of BD diagnosis on the prevalence across all studies, and this demonstrated that the classification used to diagnose BD had no significant effect on the prevalence of pain ($b1 = 0.310$, $z = 0.524$, P = 0.59).

Comparing the prevalence of pain in people with BD versus control groups

In each of the seven studies with a control group, persons with bipolar disease consistently reported a higher prevalence of pain than the comparison group. One study (33) provided pain data for two different types of pain and was corrected for multiple comparisons in the pooled analysis. In total, data from 12 342 577 unique individuals (n with BD = 138 285 and control n = 12 204 292) indicated that the RR of pain in people with BD was 2.14 [95% CI = 1.67–2.75%, χ^2 = 36.623 (df = 1), $P < 0.0001$; Cochran Q = 1078.49 (df = 7), $P < 0.0001$]. The results from the meta-analysis are presented in Fig. 3. The funnel plot of the seven included studies was not symmetrical indicating possible publication bias. However, the Eggers test (10.931, P = 0.013), but not the Begg–Mazumdar: test (Kendall's $\tau = 0.14$; P = 0.7195), showed evidence of publication bias.

Pooled prevalence of migraine in people with BD

We also calculated the pooled prevalence of migraine in 127 905 individuals across nine studies (8, 32, 39, 40, 42–44, 47, 52), and this yielded a prevalence of 14.2% [95% CI = 10.6–18.3%; Cochran Q = 1080.29 (df = 8), $P < 0.0001$].

Comparing the prevalence of migraine in people with BD versus control groups

It was possible to pool the data from three comparative studies (8, 44, 52) involving 6 732 220 unique individuals (n with BD = 126 956, n controls = 6 605 264). The RR was 3.30 (95% CI = 2.27–4.80%, χ^2 = 39.408 (df = 1), $P < 0.0001$).

Table 2. Results of pain in included studies

Study	Type of pain	Method of pain assessment/ascertainment	Pain results BD	Pain results in control	Other results
8	Arthritis Back pain Chronic Pain Migraine Other headache Psychogenic Neuropathic	ICD-9-CM based on electronic patient records	Total n = 96 186 in BD sample Any pain 61.3% (n = 58 983) Arthritis 45.3% (n = 43 595) Back pain 33.5% (n = 32 264) Chronic pain 3.4% (n = 3316) Migraine 4.9% (n = 4677) Other Headache 6.7% (n = 6419) Psychogenic pain 0.9% (n = 833) Neuropathic pain 5.4% (n = 5180)	Total n = 4 247 684 in control sample Any pain 42.3% (n = 1 795 600) Arthritis 32.2% (n = 1 365 901) Back pain 17.0% (n = 721 372) Chronic pain 0.7% (n = 27 758) Migraine 1.1% (n = 46 015) Other headache 2.0% (n = 86 126) Psychogenic pain 0.1% (n = 3646) Neuropathic pain 3.7% (n = 156 393)	OR comparing BD and controls: Any pain OR 2.17 (CI 2.14–2.19%)* Arthritis OR 1.75 (CI 1.73–1.77%)* Back pain OR 2.47 (CI 2.43–2.50%)* Chronic pain OR 5.43 (CI 5.23–5.63%)* Migraine OR 4.67 (CI 4.53–4.82%)* Other headache OR 3.46 (CI 3.37–3.55%)* Psychogenic pain OR 10.17 (CI 9.43–10.96%)* Neuropathic pain OR 1.49 (CI 1.45–1.53%)*
32	Migraine	Physician diagnosis	33.9% (n = 115) had migraines	No Control Group	Migraine group higher nr of psychiatric comorbidity (72.6%) vs. non migraine group (47.4%), $P < 0.001$ Migraine group more likely to have anxiety disorder ($P < 0.001$) and depressive polarity
33	LBP Headache	Elixhauser Comorbidity Index	25.8% (n = 919/3557) had LBP 19.3% (n = 685/3557) headaches	13.3% (n = 96 201/726 262) had LBP 5.7% (n = 41 234/726 262) headaches	BD more likely to have LBP ($P < 0.0001$) and headaches ($P < 0.0001$)
34	Chronic pain interfering with ADL	Single item question	46% (n = 338/641) had chronic pain interfering with ADL	No control group	
35	(i) migraines and (ii) body aches	Self-report 4 point Likert scale questions rating pain during depressive episode	68.5% sample (46/67) had headaches; 29.9% slight, 20.9% moderate and 17.9% major problem 62.6% sample had body aches; 22.4% slight, 19.4% moderate, and 20.9 major problems	No control group	Current BDRS score predicted headaches ($P = 0.012$)* BDRS severity not related to body aches $P = 0.3$
36	General pain	VAS interviewer administered to assess pain over last 6 weeks (>40 on VAS) Noted severity, duration, and interference with ADL	51.2% (n = 62/121) had pain Duration of pain 62.5 (±90.9) months Severity 67.5 (±14.9) Interference with ADL 67.7 (±21.2) Location of pain: Head 66.1%; Neck 66.1%; Back 74.2%; Limbs 67.7%; Joints 64.5% Nr. of pain locations: 3.44 (±1.46) 75% of pain musculoskeletal pathology	No control group	Older age associated with pain (OR 1.03 (CI 1.00–1.07%) Sex, education, marital status, diagnostic group, depressed mood, sleep disorders, and depression not related to pain
37	Painful somatic symptoms	Medical records	22.6% (n = 56/248)	No control group	
38	General pain interfering with activities	Single item question about pain interfering with ADL over past 4 weeks (0 = not at all to 5 = extremely)	24.8% (n = 219/883) had moderate or worse pain interfering with ADL	11.9% (n = 5023/42 210) had moderate or worse pain interfering with ADL $P < 0.001$	Comorbid anxiety (OR 1.72, 95% CI 1.41–2.10%), being married (OR 1.33, 95% CI 1.08–1.64%), and SUD (OR 1.91, 95% CI 1.56–2.34%) associated with interfering pain. Age, lower income associated with pain ($P < 0.001$)*
39	Migraine	Unclear, searched patient records	4.7% (n = 8/169)	No control group	
40	Migraine/headache	ICHD-2	70% (n = 7/10) had migraine	No control group	
41	LBP	LBP classified as present yes/no from national patient electronic records database	15.4% (n = 663/4310) had LBP	10.6% (n = 361 868/3 408 760), $P < 0.0001$	BD more likely to have LBP ($P < 0.0001$)*

Table 2. (Continued)

Study	Type of pain	Method of pain assessment/ascertainment	Pain results BD	Pain results in control	Other results
42	Migraine	Question on lifetime prevalence of migraine	39.8% (n = 43/108) had lifetime prevalence of migraine	No control group	Number of psychiatric admission higher in BD without migraine (P = 0.046)*, no difference in suicide attempts or SUD
43	Migraine/headache	Physician diagnosed and classified	20% (n = 6/30) migraine 33.3% (n = 10/30) muscle tension headache	No control group	
44	Migraine	Survey on previous diagnosis by physician	14.9% for males and 34.7% for females had migraines	5.8% for men and 14.7% females had migraines	BD males with migraine more likely to report earlier BD onset (P < 0.05)*, and anxiety (P < 0.05)*
45	Arthritis/chronic pain	Single item self-report question	48.9% (n = 188/384) had chronic pain	No control group	Chronic pain associated with worse physical HRQOL (P < 0.001)* but better mental HRQOL scores (P = 0.01)*
46	Joint pain	Check list	18.5% (n = 5/27) had joint pain	No control group	
47	Migraine	ID migraine questionnaire according to International Headache Society	23.9% (n = 71/296) had migraine	No control group	Migraine associated with BD diagnostic subtype (P < 0.001)*, History suicidal behaviour (P = 0.03)*, social phobia 7 panic disorder (P < 0.001)*, OCD, and anxiety (P < 0.001)*
48	Medically unexplained pain (MUS)	Asked if has pain lasting >6 months in past year that was severe/interfered with ADL and could not be explained	0.3% had severe chronic pain interfering with ADL (n = 190/6328) OR 5.93 (1.71–20.60)	No control group data	
49	Chronic pain	GP database ≥4 analgesic prescriptions in last year OR ≥4 antiepileptics in the absence of an epilepsy	17.5% (n = 451/2582) had chronic pain	8.8% (n = 125 680/1 421 796) had chronic pain	OR 1.88 P < 0.001 Chronic pain in BD vs. control*
50	Chronic pain	Modified CIDI checklist for medical disorders	40.4% (n = 38/93) had chronic pain	Not reported	BD associated with chronic pain OR 3.0 (CI 1.5–5.8%), P < 0.001*
51	General pain	Classified from medical records present = yes/no	18.1% had pain (n = 4381/24 206)	No control group	
52	Migraine	Defined from medical records	2.0% migraine (n = 530/27 054)	0.7% (n = 16 383/2 325 247)	

BD = bipolar disorder; VAS = visual analogue scale; ADL = activities of daily living; ICHD-2 = International Classification of Headache Disorders, 2nd edition; LBP = low back pain; SF 36 = short form 36; nr = number; SUD = substance use disorder; BDRS = Bipolar Depression Rating Scale; OCD = obsessive compulsive disorder.
*Statistically significant.

Pooled prevalence of chronic pain in people with BD

It was possible to calculate the pooled prevalence of chronic pain in 106 214 individuals with BD across six studies (8, 34, 45, 48–50). The pooled prevalence of chronic pain was 23.7% [95% CI = 13.1–36.3%, Cochran Q = 2200.77 (df = 5), $P < 0.0001$]. Only two comparative studies (8, 49) contained data on chronic pain, and it was therefore not possible to meta-analyze these data.

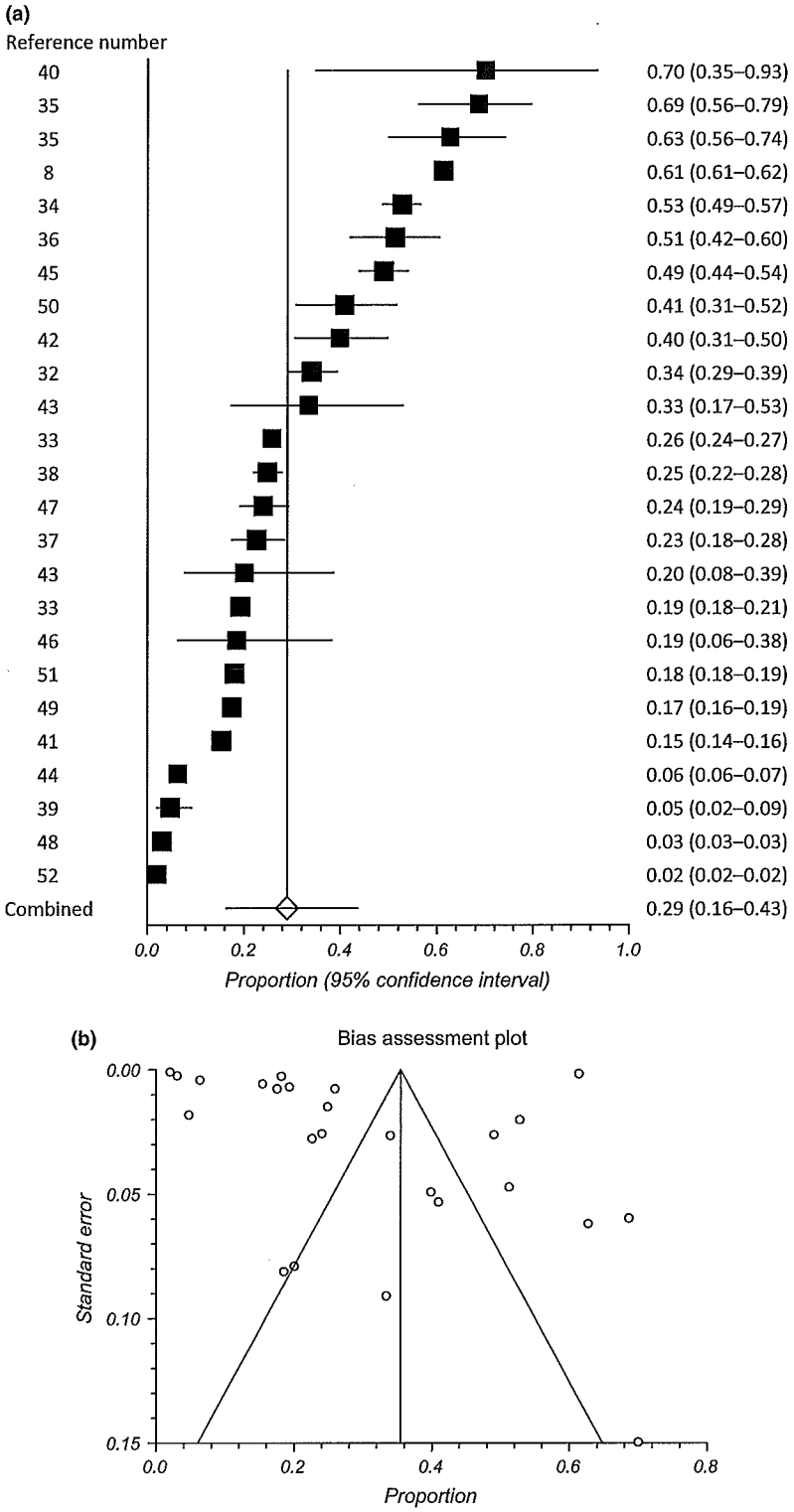

Fig. 2. Random effects pooled prevalence of pain in bipolar samples ($N = 22, n = 171\ 352$). Pooled proportion = 28.9% (95% CI = 16.4–43.4%). Cochran Q = 66988.29 (df = 24), $P < 0.0001$. (b) Funnel plot. Begg–Mazumdar: Kendall's $\tau = -0.013$, $P = 0.90$; Egger: bias = 11.510, $P = 0.48$.

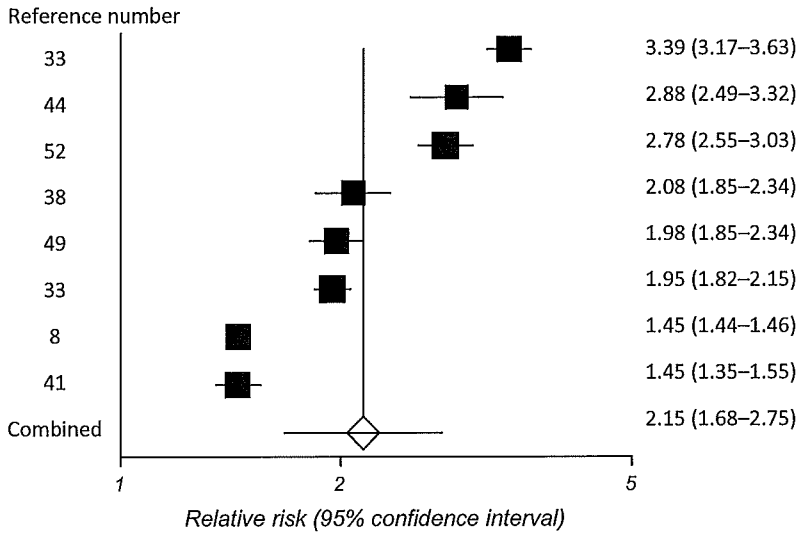

Fig. 3. Relative risk (RR) of pain in people with bipolar disorder compared *t* controls ($N = 7$, $n = 12\ 342\ 577$). Pooled RR = 2.14 (95% CI = 1.676–2.75%), $\chi^2 = 36.623$ (df = 1), $P < 0.0001$; Cochran $Q = 1078.49$ (df = 7), $P < 0.0001$.

Discussion

To our knowledge, this is the first systematic review and meta-analysis investigating the prevalence of pain in people with BD. In this large review involving 171 352 persons with BD and 12 204 292 controls, we found that a substantial proportion of patients with BD reported clinically relevant levels of pain. The overall pooled analysis of pain in people with BD was 28.9%, and the RR was over double for people with BD compared to members of the general population. In terms of specific types of pain, the pooled prevalence of chronic pain was high with almost one in four (23.7%) being affected. In addition, migraine affected one in seven (14.2%) persons with BD, and the comparative analysis demonstrated that people with BD are over three times more likely to experience migraines than members of the general population.

Increased levels of pain in persons with BD may be explained by several mechanisms. For instance, BD and migraine appear to share some specific polymorphisms, with the KIAA0564 gene being particularly implicated, thus suggesting a close association (53, 54). Also, people with BD have an increased prevalence of depression (8, 36), and depression has been associated with increased physical complaints, and possibly, greater pain sensitivity (55), opposite to findings in schizophrenia (19). For example, neuroimaging studies in major depressive disorder indicate that heightened amygdala activity, in part, explains the high comorbidity of pain and depression when these conditions become chronic (56). However, due to limitations in the available data, we could not investigate the influence of depressive symptoms on the observed results. Other studies have suggested serotonergic and noradrenergic pathway involvement (7, 57). In addition, specific neuroinflammatory mechanisms responsible for an elevated risk of painful physical comorbidity in people with BD may contribute to the higher levels of observed pain (58). Previous research (59) has found that migraine and BD symptoms are closely related, and the presence of migraine can influence pain perception. As we found that 14.2% of people with BD experienced migraine, this could have influenced the variance in the prevalence of pain. Lastly, recent findings (60) also suggest that limited cognitive flexibility and memory capacities may be linked to the mechanisms of pain chronicity and probably also to its neuropathic quality. This may imply that people with BD who are known to have deficits in executive functioning or memory have a greater risk of pain chronicity after a painful event. This seems particularly pertinent given the fact that we found across 106 214 individuals with BD that almost one in four is affected by chronic pain.

Clinical implications

The results of this review are concerning because pain and in particular chronic pain in people with BD is associated with impaired recovery (45), greater functional incapacitation (44, 61), lower quality of life (8), and increased risk of suicide compared to people without pain (62). As BD is already associated with a greatly increased risk of suicide (63), it is imperative that this population receives adequate pain assessment and management (36). A central component to this is the training and education of psychiatrists who are in a

critical place to oversee the pharmacological management of pain (7). We advocate that systematic assessment of pain should be undertaken as part of the management of BDs and that pain should be monitored during the course of treatment. Equally, healthcare professionals dealing with pain should consider mental health complications. Previous work suggests that clinicians are more likely to attend to pain than mental distress (64). The potential benefits of early identification and treatment of pain may not only include a reduction in pain and of its impact on the individual, but may also extend to a reduction of healthcare costs and improvement of mental health outcomes.

Of great concern are the high levels of chronic pain experienced by people with BD. A better understanding of the association of BD and chronic pain could help limit harmful/adverse pharmacological side-effects. For instance, in the general population, chronic pain is often managed with tri-cyclical antidepressants (65), yet prescription of such medication to a person with BD may inadvertently trigger a manic phase of illness if prescribed in the absence of a mood stabilizer (66). Commonly used analgesic medications also need careful consideration. For instance, there is sound evidence that non-steroidal anti-inflammatory medications can increase serum lithium levels, impairing renal lithium excretion and possibly eliciting lithium toxicity (67). Similarly, some stronger analgesic medications such as opioids may have mood altering qualities increasing the risk of eliciting a manic episode (68).

Limitations of the review

Several limitations, especially of the included literature need to be considered when interpreting the results of our review. First, BD is a complex and heterogeneous disorder, and reporting of pain likely varies according to different phases, polarity and acuity of the disease. The paucity of information regarding these illness characteristics made it impossible to systematically evaluate their effects on pain prevalence in patients with BD. In addition, the perception and therefore prevalence of pain is known to vary according to the type of BD (I or II) (59), but due to limitations in the data, we were not able to disentangle this relationship. In addition, gender may also cause some variance, but our moderator analysis did not elucidate any evidence of a gender effect. Second, all of the included studies utilized a cross-sectional measurement of pain and did not correlate pain with mood state or severity of symptoms. Therefore, prospective longitudinal studies that assess pain prevalence and severity over time and in relationship to mood symptoms and treatments are essential. Third, our results may have been suspect to *Berkson's bias,* which states that clinical samples are more impaired and experience more pain than non-clinical samples due to self-referral to a clinical setting. *Berkson's bias* has been observed in the mood dimensions of BD (69) and may account for an underreporting within the pooling of epidemiological data. Fourth, none of the included studies used a validated pain assessment scale, and subsequent information about the severity, location, variability, and interference of pain during activities is lacking. Fifth, all of the meta-analytic results were heterogeneous. and some demonstrated a degree of publication bias. In our moderator analysis, we were not able to explain the heterogeneity with mean age, % males, or the methodological quality of method of classification of BD. This finding demonstrates that unknown/unmeasured factors contribute to the observed heterogeneity. Regarding publication bias, the funnel plot for the main analysis (Fig. 2b) appeared asymmetrical, yet the quantitative investigation of bias did not demonstrate any evidence to support this. This discrepancy may be due to the fact that there is a trend for publication bias, but its magnitude is insufficient to reach statistical significance according to the Eggers test or Begg–Mazumdar test. In addition, the comparative analysis (Fig. 3) demonstrated some publication bias with the Eggers test, but this finding should be interpreted with caution due to the low number of studies (<10) (70). Sixth, there was insufficient information about psychotropic and analgesic medication within the BD cohorts to enable statistical investigation of these variables on the observed results. Future research should seek to investigate the influence of psychotropic and analgesic medications on pain, and particular attention should be paid to the prevalence of pain in people with BD who are drug naïve. In the same way, future research should investigate the role of psychiatric comorbidities including anxiety and substance use disorders on the prevalence of clinical pain in these patients. Finally, we included 15 studies that received low methodological quality ratings. However, the low methodological quality ratings were due to the absence of a control group, and the moderator analysis demonstrated that these studies had no significant effect on the observed results. Despite the aforementioned, higher levels of pain were reported consistently among people with BD than in the comparison groups.

Future research

It is essential that future research seeks to clearly assess pain characteristics including noting the site, severity, variability, and chronicity. There were insufficient data to analyze these pain characteristics in our meta-analysis. In addition, only one study (8) measured psychogenic pain, and it would be important to investigate if this differs from physiological pain in people with BD. An important question, also unaddressed, is what is the impact of comorbid pain, particularly chronic pain, on daily activities? It is likely that chronic pain amplifies the effect of BD on disability and reduced quality of life. Future prospective studies should be conducted in order to truly capture the prevalence of pain and disentangle its impact and contributing factors. Such research should establish how pain impacts on a person's mental health and wellbeing, with longitudinal studies being most important. Future research should also explore the extent to which those with BD are more or less responsive to behavioural, pharmacological, and non-pharmacological treatments for pain. For example, studies have not yet examined the impact on pain of antiepileptic medications such as lamotrigine, valproate, and topiramate among persons with BD. In addition, in the general population the promotion of physical activity is a key factor preventing the onset of chronic pain but is also encouraged to treat it (71), and many people with chronic pain are inactive (72). However, research (73) has established that most people with BD are sedentary. Therefore, strategies to encourage people with BD to become active that do not exacerbate their pain are likely to be key in the prevention and management of pain and physical therapists can lead this process (74). In addition, the barriers and facilitators to pain management should be explored in people with BD with emphasis on the perspective of the patient and the treating multidisciplinary team. Lastly, within our review, there were limited studies assessing pain in patients with BD and those with other psychiatric conditions, making it impossible to directly compare the prevalence of clinical pain in people with BD and other psychiatric diagnosis. More research is required to directly compare clinical pain across different psychiatric disorders.

To conclude, almost 30% of persons with BD experience clinically relevant pain, which was twice as common compared to general population controls. Chronic pain was prevalent affecting almost one in four people, and migraine was over three times as common than in the general population. Pain has a range of adverse and deleterious impact upon the individual and may impede recovery, reduce quality of life and have adverse effects on psychiatric symptoms. Therefore, it is essential that treating psychiatrists and the wider multidisciplinary team seek to provide adequate assessment and treatment of pain in people with BDs.

Declaration of interest

BS, AJM, AS, SR, and LE have no conflicts of interest to declare. DV is supported by the Research Foundation – Flanders (FWO – Vlaanderen). MDH declares that he has been a consultant for, received grant and/or research support and honoraria from, and been on the speakers' bureaus and/or advisory boards of the following companies: Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Pfizer, Sanofi Aventis, and Takeda. CUC has been a consultant and/or advisor to or has received honoraria from: Actelion, Alexza; Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, Medavante, Medscape, Merck, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Takeda, Teva, and Vanda. He has received grant support from BMS, Janssen/J&J, Novo Nordisk A/S, and Otsuka.

References

1. IASP. Why pain control matters in a world of killer disease. Available from http://www.iasp-pain.org/AM/Template.cfm?Section=Press_Release&Template=/CM/ContentDisplay.cfm&ContentID=2911, (last accessed on January 28, 2014).
2. Murray CJL, Vos T, Lozano R et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;**380**:2197–2223.
3. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;**10**: 287–333.
4. Arnow BA, Hunkeler EM, Blasey CM et al. Comorbid depression, chronic pain, and disability in primary care. Psychosom Med 2006;**68**:262–268.
5. Katon W, Lin EHB, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 2007;**29**:147–155.
6. Means-Christensen AJ, Roy-Byrne PP, Sherbourne CD, Craske MG, Stein MB. Relationships among pain, anxiety, and depression in primary care. Depress Anxiety 2008;**25**:593–600.
7. Elman I, Zubieta J-K, Borsook D. The missing p in psychiatric training: why it is important to teach pain to psychiatrists. Arch Gen Psychiatry 2011;**68**:12–20.
8. Birgenheir DG, Ilgen MA, Bohnert ASB et al. Pain conditions among veterans with schizophrenia or bipolar disorder. Gen Hosp Psychiatry 2013;**35**:480–484.
9. De Hert M, Correll CU, Bobes J et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011;**10**:52–77.
10. Leucht S, Burkard T, Henderson J, Maj M, Sartorius N. Physical illness and schizophrenia: a review of the literature. Acta Psychiatr Scand 2007;**116**:317–333.

11. Stubbs B, De Hert M, Sepehry AA et al. A meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia. Acta Psychiatr Scand 2014;**130**:470–486.
12. Prieto ML, Cuéllar-Barboza AB, Bobo WV et al. Risk of myocardial infarction and stroke in bipolar disorder: a systematic review and exploratory meta-analysis. Acta Psychiatr Scand 2014;**130**:342–353.
13. De Hert M, Cohen D, Bobes J et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry 2011;**10**:138–151.
14. Mitchell AJ, Malone D, Doebbeling CC. Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies. Br J Psychiatry 2009;**194**:491–499.
15. Mitchell AJ, Lord O, Malone D. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. Br J Psychiatry 2012;**201**:435–443.
16. Kilbourne AM, McCarthy JF, Welsh D, Blow F. Recognition of co-occurring medical conditions among patients with serious mental illness. J Nerv Ment Dis 2006;**194**: 598–602.
17. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, de Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. Psychol Med 2012;**42**:125–147.
18. RETHINK. Lethal discrimination. 2013. Last accessed 1st February 2014.
19. Engels G, Francke AL, van Meijel B et al. Clinical pain in schizophrenia: a systematic review. J Pain 2013;**10**: 191–196.
20. Dilsaver SC, Benazzi F, Manning JS, Akiskal KK, Akiskal HS. Pain complaints in Latino adults of Mexican origin with and without major depressive episode: a cross-sectional study. Prim Care Companion J Clin Psychiatry 2008;**10**:191–196.
21. Fornaro M, de Berardis D, Iasevoli F et al. Treatment adherence towards prescribed medications in bipolar-II acute depressed patients: relationship with cyclothymic temperament and "therapeutic sensation seeking" in response towards subjective intolerance to pain. J Affect Disord 2013;**151**:596–604.
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Clin Trials 2009;**6**:1–6.
23. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders – DSM-IV-TR, 4th edn. New York: American Psychiatric Association, 2000.
24. World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders – Diagnostic Criteria for Research. Geneva, Switzerland: World Health Organisation, 1993.
25. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;**30**:473–483.
26. Wells G, Shea B, O'Connell D, Peterson JEA. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (last accessed on December 12, 2013).
27. Stubbs B, West E, Patchay S, Schofield P. Is there a relationship between pain and psychological concerns related to falling in community dwelling older adults? A systematic review. Disabil Rehabil 2014;**36**:1931–1942.
28. Dersimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;**7**:177–188.
29. Hedges LV. Statistical models for meta-analysis. New York: Academic Press, 1985.
30. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;**50**:1088–1101.
31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**:629–634.
32. Brietzke E, Moreira CLRL, Duarte SVB et al. Impact of comorbid migraine on the clinical course of bipolar disorder. Compr Psychiatry 2012;**53**:809–812.
33. Carney CP, Jones LE. Medical comorbidity in women and men with bipolar disorders: a population-based controlled study. Psychosom Med 2006;**68**:684–691.
34. Cerimele JM, Chan Y-F, Chwastiak LA, Unützer J. Pain in primary care patients with bipolar disorder. Gen Hosp Psychiatry 2014;**36**:228.
35. Ehnvall A, Mitchell PB, Hadzi-Pavlovic D et al. Pain and rejection sensitivity in bipolar depression. Bipolar Disord 2011;**13**:59–66.
36. Failde I, Dueñas M, Agüera-Ortíz L, Cervilla JA, Gonzalez-Pinto A, Mico JA. Factors associated with chronic pain in patients with bipolar depression: a cross-sectional study. BMC Psychiatry 2013;**13**:112.
37. Fornaro M, Maremmani I, Canonico PL et al. Prevalence and diagnostic distribution of medically unexplained painful somatic symptoms across 571 major depressed outpatients. Neuropsychiatr Dis Treat 2011;**7**:217–21.
38. Goldstein BI, Houck PR, Karp JF. Factors associated with pain interference in an epidemiologic sample of adults with bipolar I disorder. J Affect Disord 2009;**117**: 151–156.
39. Holland J, Agius M, Zaman R. Prevalence of co-morbid bipolar disorder and migraine in a regional hospital psychiatric outpatient department. Psychiatr Danub 2011;**23** (Suppl 1):S23–S24.
40. Hung C-I, Liu C-Y, Wang S-J. Migraine predicts physical and pain symptoms among psychiatric outpatients. J Headache Pain 2013;**14**:19.
41. Kilbourne AM, Cornelius JR, Han X et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord 2004;**6**:368–373.
42. Low NCP, du Fort GG, Cervantes P. Prevalence, clinical correlates, and treatment of migraine in bipolar disorder. Headache 2003;**43**:940–949.
43. Marchesi C, de Ferri A, Petrolini N et al. Prevalence of migraine and muscle tension headache in depressive disorders. J Affect Disord 1989;**16**:33–36.
44. McIntyre RS, Konarski JZ, Wilkins K, Bouffard B, Soczynska JK, Kennedy SH. The prevalence and impact of migraine headache in bipolar disorder: results from the Canadian Community Health Survey. Headache 2006;**46**:973–982.
45. Miller CJ, Abraham KM, Bajor LA et al. Quality of life among patients with bipolar disorder in primary care versus community mental health settings. J Affect Disord 2013;**146**:100–105.
46. Mitchell P, Parker G, Jamieson K et al. Are there any differences between bipolar and unipolar melancholia? J Affect Disord 1992;**25**:97–105.
47. Ortiz A, Cervantes P, Zlotnik G et al. Cross-prevalence of migraine and bipolar disorder. Bipolar Disord 2010; **12**:397–403.

48. Park S, Cho MJ, Seong S et al. Psychiatric morbidities, sleep disturbances, suicidality, and quality-of-life in a community population with medically unexplained pain in Korea. Psychiatry Res 2012;**198**:509–515.
49. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC Med 2013;**11**:263.
50. Subramaniam M, Abdin E, Vaingankar JA, Chong SA. Prevalence, correlates, comorbidity and severity of bipolar disorder: results from the Singapore Mental Health Study. J Affect Disord 2013;**146**:189–196.
51. Walid MS, Zaytseva N. Pain in nursing home residents and correlation with neuropsychiatric disorders. Pain Physician 2009;**12**:877–880.
52. Weber NS, Fisher JA, Cowan DN, Niebuhr DW. Psychiatric and general medical conditions comorbid with bipolar disorder in the national hospital discharge survey. Psychiatr Serv 2011;**62**:1152–1158.
53. Oedegaard KJ, Greenwood TA, Johansson S et al. A genome-wide association study of bipolar disorder and comorbid migraine. Genes Brain Behav 2010;**9**:673–680.
54. Wei X, Cohen-Woods S, Qian C et al. Genome-wide association study of bipolar disorder in Canadian and UK populations corroborates disease loci including SYNE1 and CSMD1. BMC Med Genet 2014;**15**:1–26.
55. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;**163**:2433.
56. Strigo IA, Simmons AN, Matthews SC, Craig ADB, Paulus MP. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. Arch Gen Psychiatry 2008;**65**:1275–1284.
57. Clark MR. Psychopharmacology of chronic pain. Prim Psychiatry 2007;**14**:70–79.
58. Leboyer M, Soreca I, Scott J et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 2012;**141**:1–10.
59. Oedegaard KJ, Angst J, Neckelmann D, Fasmer OB. Migraine aura without headache compared to migraine with aura in patients with affective disorders. J Headache Pain 2005;**6**:378–386.
60. Attal N, Masselin-Dubois A, Martinez V et al. Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. Brain 2014;**137**:904–917.
61. Hirschfeld RMA, Calabrese JR, Weissman MM et al. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;**64**:53–59.
62. Ratcliffe GE, Enns MW, Belik S, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. Clin J Pain 2008;**24**:204–210.
63. Novick DM, Swartz HA, Frank E. Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. Bipolar Disord 2010;**12**:1–9.
64. Jacobsen PB, Shibata D, Siegel EM et al. Evaluating the quality of psychosocial care in outpatient medical oncology settings using performance indicators. Psychooncology 2011;**20**:1221–1227.
65. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev 2007;CD005454.
66. Pacchiarotti I, Thase ME, Souery D et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013;**170**:1249–1262.
67. Ragheb M. The clinical significance of lithium-nonsteroidal anti-inflammatory drug interactions. J Clin Psychopharmacol 1990;**10**:350–354.
68. Martins SS, Keyes KM, Storr CL, Zhu H, Chilcoat HD. Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend 2009;**103**:16–24.
69. Regeer EJ, Krabbendam L, de Graaf R, ten Have M, Nolen WA, van Os J. Berkson's bias and the mood dimensions of bipolar disorder. Int J Methods Psychiatr Res 2009; **18**:279–286.
70. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
71. National Institute for Health and Clinical Excellence NIFHAC, NICE. Early management of persistent non-specific low back pain. NICE clinical guideline 88.
72. Stubbs B, Binnekade TT, Soundy A, Schofield P, Huijnen IPJ, Eggermont LHP. Are older adults with chronic musculoskeletal pain less active than older adults without pain? A systematic review and meta-analysis. Pain Med 2013;**14**:1316–1331.
73. Janney CA, Fagiolini A, Swartz HA, Jakicic JM, Holleman RG, Richardson CR. Are adults with bipolar disorder active? Objectively measured physical activity and sedentary behavior using accelerometry. J Affect Disord 2014;**152–154**:498–504.
74. Stubbs B, Probst M, Soundy A et al. Physiotherapists can help implement physical activity programmes in clinical practice. Br J Psychiatry 2014;**204**:164.