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History of Bipolar disorder and the risk of dementia: a systematic review and meta-analysis

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Abstract

Objective—We carried out a systematic review and meta-analysis to evaluate whether history of bipolar disorder increases the risk of dementia.

Design—Systematic review and meta-analysis of the literature.

Method—We searched Pubmed and Scopus to identify studies that evaluated the risk of dementia in individuals with a history of bipolar disorder. A total of 6 studies including 3026 individuals with history of bipolar disorder and 191,029 non-bipolar disorder individuals were included in the meta-analysis.

Results—History of bipolar disorder significantly increased the risk of diagnosis of dementia (pooled odds ratio = 2.36 CI_{95%} (1.36-4.09), $z=3.07$, $p<0.001$). There was evidence of heterogeneity and of publication bias in the analysis.

Conclusion—History of bipolar disorder is associated with significantly higher risk of dementia in older adults. Future studies are necessary to evaluate the potential mediators of this association as well as to evaluate interventions that may reduce the risk of dementia in this population.

Keywords

Bipolar disorder; Dementia; Alzheimer's disease; Risk factor

Introduction

Bipolar disorder (BD) is a common and disabling condition in the general population, with lifetime prevalence rates ranging from 0.8% to 2% for BD type 1 and type 2 (1). In recent

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years, cognitive impairment has been increasingly recognized as an integral part of the BD phenotype. Several studies have shown that young and older adults with BD have significant cognitive impairment, especially with executive function and attentional processing, compared to age-matched control participants (2,3). The presence of cognitive impairment has been associated with greater disability, and it has been proposed that cognitive impairment may be a marker of neuroprogression (that is, a progressive condition that leads to cognitive impairment and dementia) in BD patients (4,5). Nonetheless, recent longitudinal studies do not corroborate this view since they failed to demonstrate accelerated cognitive decline in BD compared to age-matched controls, despite the fact that persons with BD performed worse than control participants at all study assessment points (6,7).

Another important question related to cognitive impairment in BD is whether it leads to increased risk of dementia. In contrast to major depression, there is limited and scattered information about the relationship between BD and dementia. Registry-based studies have shown that history of BD increases the risk of diagnosis of dementia (8,9), but that has not been confirmed by longitudinal studies (10).

To date no meta-analysis has specifically evaluated the risk of dementia in patients with a history of BD. The confirmation of the association between BD and future risk of dementia would favor the neuroprogression hypothesis of BD since dementia can be viewed as an end-stage consequence for different brain disorders. Therefore, we have carried out a systematic review and meta-analysis to estimate pooled risk of dementia in patients with BD. Our primary hypothesis was that individuals with a past diagnosis of BD would have an increased risk of dementia compared to those without BD diagnosis.

Methods

This meta-analysis followed the PRISMA guideline for conducting and reporting systematic reviews (11). The PRISMA guideline is an evidence-based set of items for reporting in systematic reviews and meta-analyses that focus on standardization of how to conduct and report systematic reviews and meta-analyses.

Search strategy

We conducted a comprehensive search for potentially relevant studies of bipolar disorder and dementia risk in the electronic bibliographic databases PubMed and Scopus, which provide broad coverage of biomedical journals published worldwide. We limited the search to English language and papers published after 1/1/1980. We also searched references of selected publications. The literature search was conducted in June 2016. Searches included the following broad terms: bipolar disorder* (as a Medical Subject Heading (MeSH) term) AND dementia. This search retrieved a total of 1967 references. After removing duplicated hits, 1656 papers were selected for review.

Study selection and quality assessment

Two authors (BSD and FC) independently reviewed all abstracts and papers to evaluate whether the study would meet criteria for inclusion in the meta-analysis. If there was any disagreement between the authors about the inclusion of a study, a third author (ALT)

reviewed the study and made a decision about the inclusion / exclusion of the study from the meta-analysis.

After reviewing the references, we selected the studies for data extraction and analysis based on the following criteria: (a) cohort, case-control or case-registry study; (b) identification of bipolar disorder and control / comparison groups; (c) report of dementia cases in the bipolar disorder and control groups.

We used the Newcastle–Ottawa Scale (NOS) to assess the quality of each study selected for inclusion in the meta-analysis (12). This measure assesses methodological aspects of observational studies such as selection of cases and controls, comparability of population ascertainment of exposure to risk, quality of case ascertainment and outcome assessment.

Data extraction and statistical analysis

For each study included in the meta-analysis, we extracted the number of individuals with dementia in each diagnostic group to create a 2×2 table (i.e., bipolar disorder with dementia, bipolar disorder without dementia, control with dementia, and control without dementia) that allowed the calculation of pooled risk of dementia in bipolar disorder subjects compared to control subjects. Two authors (BSD and FC) independently extracted the data from included studies. If there was any disagreement between the authors about data extraction, a third author (ALT) reviewed the study and made a decision about the data extraction for inclusion in the meta-analysis.

We used DerSimonian and Laird random effects method to calculate the pooled odds ratio of dementia in BD individuals given the evidence of high heterogeneity among the studies included in the analysis (see Results section for details). Sensitivity analysis was conducted using the “leave-one-out” method to evaluate whether individual studies significantly influenced the pooled odds ratio. We evaluated publication bias by visual inspection of the funnel plot and by a classic fail-safe N analysis. All analyses were done with the Comprehensive Meta-Analysis Software v2 for Windows.

Results

The flowchart shows the selection process of articles. A total of 6 studies were included in the systematic review and meta-analysis (table 1). We included a total of 194,055 subjects (3,026 with history of bipolar disorder and 191,029 non-bipolar disorder individuals). Most studies were of moderate methodological quality. Although the sample size of the bipolar and non-bipolar groups is unbalanced, the prevalence rate of bipolar disorder in the pooled sample is 1.5%, similar to what is observed in population-based epidemiological studies (1).

We found evidence of significant heterogeneity among studies ($Q=70.70$, $df=5$, $p<0.001$; $I^2=93\%$), and thus we used random effect models to calculate the pooled risk of dementia in BD. The pooled odds ratio of dementia in BD individuals was 2.36 $CI_{95\%}$ (1.36 - 4.09) (Figure 1). Sensitivity analysis showed that no single study significantly influenced the analysis (see supplementary figure 1). The visual inspection of the funnel plot showed

evidence of significant publication bias that was confirmed statistically by the classic fail-safe N analysis ($z=11.6$, $P<0.001$) (see supplementary figure 2).

Discussion

To the best of our knowledge, this is the first meta-analysis evaluating the risk of dementia in individuals with a history of bipolar disorder. We found that a history of bipolar disorder significantly increases the risk of dementia in older adults. Our results provide robust evidence that mood disorders in general, and not only major depressive disorders, are associated with increased risk of dementia (17,18). Given the limited number of long-term longitudinal, well-controlled studies of progressive cognitive changes in BD, our meta-analysis provides additional evidence that bipolar disorder can be viewed as a progressive condition that leads to cognitive impairment and dementia, at least in a subgroup of individuals. Finally, the association between bipolar disorder and risk of dementia is consistent across studies conducted around the world, making the association even more credible.

The estimated risk of dementia in bipolar disorder is larger than reported in meta-analyses of unipolar major depression (risk estimates ranging from 1.65 to 2.0 (17,18). This raises the question of whether there are different mediators of dementia risk between unipolar and bipolar patients. Although unipolar depression and bipolar disorder share abnormalities in several neurobiological pathways, in particular high, pro-inflammatory activity, reduced neurotrophic support, and high oxidative stress burden, there may be unique features for bipolar disorder (19,20). By definition, bipolar patients experience manic and/or hypomanic episodes whose neurobiological underpinnings may contribute unique factors adding to risk. For most patients, bipolar disorder is a more severe illness, in which greater levels of medical comorbidity (obesity, diabetes, sleep apnea), worse health related behaviors (diet, exercise, smoking, risky sexual behaviors), and substance abuse and worse cognitive function (21-23) may lead to lower brain and cognitive reserve, thereby increasing risk of clinical dementia. Finally, intrinsic factors related to bipolar disorder, in particular its genetic susceptibility, may render patients more susceptible to progressive brain changes and cognitive impairment (24). The interaction among these factors, thus, can put bipolar patients at increased risk of developing dementia later in life compared to patients with unipolar depression. Longitudinal studies, including the collection of clinical and biological measures are necessary to evaluate the potential mechanisms by which bipolar disorder can increase the risk of dementia later in life.

Patients with bipolar disorder have increased risk of premature death related to general medical conditions and to suicide (25, 26) Recent studies suggest that suicide attempters are at higher risk of cognitive impairment and, as a consequence, higher risk of dementia (27, 28). The studies included in this meta-analysis did not evaluate the competing effect of premature death on the risk of dementia ("survivor effect"). One important consequence is that the association between bipolar disorder and dementia may have been weakened in the original studies and, as a consequence, in the current meta-analysis.

The current results should be viewed in light of study limitations. Most of the studies included for data extraction were registry-based studies and were of moderate methodological quality. Results from registry-based studies have several limitations, including lack of control by the researchers about how data were collected, in particular how the diagnosis of bipolar disorder and dementia was attained, use of different definitions for bipolar disorder and dementia, as well as lack of information about confounders. Also, we were not able to carry out analyses with specific dementia diagnosis which limits the interpretation of the results. We were not able to evaluate whether variables like number of manic or depressive episodes, age of onset of bipolar disorder, and medical and psychiatric comorbidities moderated the risk of dementia in bipolar disorder. These are very important clinical factors since it is hypothesized that the higher the number of affective episodes, the earlier the age of onset, and the greater medical and psychiatric comorbidities, the greater the risk of cognitive impairment and dementia that may be observed in these patients.

The studies included in the meta-analysis did not control for exposure to mood stabilizers, in particular lithium carbonate. Several lines of evidence support the neuroprotective effect of lithium and its potential to modulate amyloid-beta and tau protein metabolism, and to reduce the incidence of Alzheimer's disease among bipolar patients (29). Finally, we found evidence of significant publication bias with tendency for the literature to report only significant associations between bipolar disorder and the risk of dementia. These factors altogether may have introduced an elevated risk for variability in the results of individual studies that was captured by statistically significant heterogeneity across the studies in the current meta-analysis. Although we used random effect models that make the standard error estimates more accurate in light of significant heterogeneity in the meta-analysis, the current meta-analysis still may have inflated the risk of dementia in individuals with bipolar disorder.

In sum, our meta-analysis provides robust evidence that bipolar disorder increases the risk of dementia in older adults. Future studies are necessary to evaluate the potential clinical and biological mediators of the risk of dementia among bipolar disorder patients.

Also, given the robust preclinical and clinical evidence that low dose lithium carbonate can have significant neuroprotective effects (30-32), future randomized clinical trials should explore whether long-term low dose lithium treatment can prevent and/or delay the progression of dementia in older adults with bipolar disorder.

Flow diagram showing the search, article selection and extraction processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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OR: Odds ratio, CI_{2.5%} and CI_{97.5%}: lower and upper limit of the 95% confidence interval of the odds ratio, respectively.

Figure 1.

Forest plot of the meta-analysis of risk of dementia in bipolar disorder individuals.

Table 1

Characteristics of the studies included in the systematic review and meta-analysis.

Author, year	Country	Study design	Criteria for Bipolar Disorder	Criteria for Dementia	Bipolar disorder individuals (N)	Non-bipolar disorder individuals (N)	Study quality
Zilkens, 2014 (13)	Australia	Case-control	ICD-8, ICD-9, ICD-10	ICD-9 / ICD-10	68	27048	Moderate
Aprahamian, 2014 (10)	Brazil	Case-control	DSM-IV	DSM-IV	106	103	Low
Chen, 2015 (14)	Taiwan	Registry-based	ICD-9	ICD-9	345	2291	Moderate
Kessing, 2003 (8)	Denmark	Registry-based	ICD-8	ICD-8	2007	81380	Moderate
Preuss, 2010 (15)	US	Registry-based	ICD-9	ICD-9	244	42695	Moderate
Almeida, 2016 (16)	Australia	Cohort / Registry-based	ICD-8, ICD-9, ICD-10	ICD-8, ICD-9, ICD-10	256	37512	High
					3026	191029	

ICD: International Classification of Disease, version 8; version 9; version 10. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, version IV.