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Research paper

Hypertension risk and clinical care in patients with bipolar disorder or schizophrenia; a systematic review and meta-analysis

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ABSTRACT

Background: A higher cardiovascular morbidity and mortality has been observed in patients with bipolar disorder (BPD) or schizophrenia, partly due to an increased risk of hypertension (HTN), or a less effective care of it. This systematic review and meta-analysis, presents a critical appraisal and summary of the studies addressing the risk of HTN, or the differences in its care, for those with schizophrenia or BPD.

Methods: Prospective studies were searched in PubMed, Embase, PsycINFO, Scopus, and the Web of Science, from database inception to June 2017. A meta-analysis was undertaken to obtain pooled estimates of the risk of HTN.

Results: Five studies reporting the risk of HTN, and five studies presenting differences in its clinical care, were identified. An increased risk of HTN was observed for BPD patients, with an overall Incidence Rate Ratio 1.27(1.15–1.40). The pooled Incidence Rate Ratio of HTN for those with schizophrenia was 0.94 (0.75 – 1.14). A poorer care of HTN (lower rates of screening, prescription, and adherence) was reported in four studies of schizophrenia, and two of BPD patients, compared to people without these conditions.

Limitations: reduced number of studies on risk and care of HTN on patients with BPD or schizophrenia.

Conclusions: Limited evidence suggests that patients with BPD have a higher risk of HTN. Patients with schizophrenia and BPD receive poor care of HTN. Understanding the risk of HTN, and the differences in its care, is essential for clinicians to reduce the cardiovascular morbidity and overall mortality of these patients.

1. Introduction

It is estimated that, 184 million disability adjusted life years (DALY), 7% of the total DALYs lost globally, are attributable to mental disorders. This represents nine million years of life lost (YLLs), and 175 million years lived with disability (YLDs) worldwide (Walker et al., 2015; Whiteford et al., 2013). The life expectancy in patients with mental disorders is reduced between one and 32 years, with cardiovascular (CV) disease being the biggest contributor to these premature deaths (Colton and Manderscheid, 2006; Viron and Stern, 2010; Walker et al., 2015). Patients with severe mental illnesses, including schizophrenia and bipolar disorder (BPD), have the highest mortality rate, among all patients with mental disorders (Walker et al., 2015). Four recent metanalyses have reported an increased risk of acute CV events for patients with schizophrenia and BPD (Fan et al., 2013; Li et al., 2014; Prieto et al., 2014; Correll et al., 2017). One explanation for the increased risk of CV events in patients with severe mental disorders could be the higher incidence of CV risk factors, such as hypertension (HTN), in this group. HTN has 40% prevalence in adults worldwide and it accounts for an estimated 13% of total annual deaths and 4% of total DALYs (WHO, 2010; Forouzanfar et al., 2015). Another possible explanation for the increased CV risk among patients with mental illness is that they have poorer access to preventive interventions including blood pressure control (Viron and Stern, 2010; Mitchell and Lawrence, 2011; Mitchell et al., 2009).

Evidence in this area is still insufficient to inform effective management of HTN in patients with schizophrenia or BPD. On one hand, the studies included in previous reviews of CV risk factors among people with mental illness did not investigate patients with schizophrenia or BPD specifically, they reported risk of HTN only when it was

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associated with other outcomes, or they had a cross sectional design (Meng et al., 2012; Pan et al., 2015; Vancampfort et al., 2015b; Vancampfort et al., 2013). On the other hand, the studies included in previous reviews on the potential inequalities in the management of HTN in people with mental illness did not assess specifically patients with schizophrenia or BPD, have included only subtypes of them, many studies did not have a comparison arm, and no studies published after 2011 have been reviewed (De Hert et al., 2011; Morrato et al., 2008; Kilbourne et al., 2008; Weiss et al., 2006; Nasrallah et al., 2006; Falissard et al., 2011). However, to our knowledge no systematic review has critically appraised and summarized the prospective studies reporting the risk of HTN in patients with schizophrenia or BPD, or comparing the management of HTN for those with and without these disorders. In order to stablish good control of CV risk, it is essential for clinicians to know if patients with a specific diagnosis of schizophrenia or BPD have a higher risk, and poorer care, for HTN, which has its own clinical management.(National Institute of Health and Care Excellence 2016) Strong evidence in this area could inform a better control of HTN, which should lead to a lower CV morbidity and mortality.

This paper will test the hypothesis that patients with schizophrenia or BPD, observed in available studies, have a higher risk of developing HTN, and receive poorer care for it, than those without each of these disorders. This systematic review and meta-analysis, presents a critical appraisal and summary of the studies that examined the risk, and differences in the clinical care, for HTN in patients with schizophrenia or BPD.

2. Methods

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria were used to undertake this review and meta-analysis (Supplement 1) (Stroup et al., 2000).

We aimed to identify studies in compliance with the following inclusion criteri:

1) Cohort study design
2) Reporting of original research data
3) Schizophrenia or BPD as exposure
4) Reporting as outcome either risk of HTN, or differences in its clinical care (including screening, diagnosis, treatment, or adherence to medication), for patients with and without schizophrenia or BPD.

Studies were excluded if they were

1) Conducted in specific patient sub-populations (e.g. patients receiving specific medication)
2) Reporting a composite outcome (e.g. metabolic syndrome) unless separate results for HTN had been provided.
3) Not prospective.

The following search strategy was used: ((("Schizophrenia"[Mesh]) OR "Bipolar Disorder"[Mesh])) AND ((("Hypertension"[Mesh]) OR hypertens*) OR blood pressure) OR high blood pressure). Studies were identified from PubMed, EMBASE, PsycINFO, Scopus, and the Web of Science, from inception of the database until the 28th June 2017. The titles and abstracts of all the references identified in the initial search were checked against the inclusion criteria. The studies cited by the papers fitting the inclusion criteria, and relevant reviews, were checked for inclusion. Similarly, the papers that have cited the studies fitting the inclusion criteria were also searched in the Web of Science and considered for inclusion. There were no restrictions on the basis of language, sample size or duration of follow-up. Authors of the studies were contacted in some cases, as similarities between articles indicated the possibility of multiple publications from the same cohort. Where studies reported results from the same population, data were taken from the longest follow-up. Two doctors (LA and IF) conducted all the searches, extracted the data using a predefined template, and assessed the quality of the studies fitting the inclusion criteria. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institute of Health (USA) was used to assess the risk of bias, and overall methodological quality, of the studies (National Institute of Health, 2016).

Meta-analyses were undertaken to obtain pooled estimates of the risk of HTN among patients with BPD and also among those with schizophrenia. A random effects model was used to estimate pooled effect size (Der Simonian and Kacker, 2007). The heterogeneity between studies was measured using I-squared index, that represents the percentage of the total variation which is due to heterogeneity rather than chance, and is preferred to other methods because it does not inherently depend on the number of studies in the meta-analysis. Given the small number of studies in our analysis I-Squared was chosen to avoid other estimates that perform poorly under such circumstances (Higgins et al., 2003). Chi-squared statistic was used to test the significance of the heterogeneity. When a study reported results as adjusted odds ratios (OR), the ORs were used as proxy of Cox hazard ratios, since the proportions of people with hypertension was relatively small, and the time unit used was narrow (Steele, 2005). Studies that reported incidence rate ratio (IRR) based on a Poisson regression model, using person-time as denominator, or hazard ratios based on Cox regression model, were combined as these estimates, have fairly similar interpretation (Sedgwick, 2012a, b). If a study that reported estimates for each age category, and for the whole sample, we included in the metanalysis the estimates obtained from the full data, in compliance with other estimates included. When a study reported estimates for each gender category separately, and not estimates based on the whole sample were reported, estimates for each gender were included in the metanalaysis independently. If a study presented results from a multivariable model exploring the association between schizophrenia or BPD and HTN, and then further models were built to explore potential explanatory factors of the association, only the results from the first multivariable model were included in the metanalysis. No attempt was made to test possible publication bias, small study effect or other irregularities, using funnel plots or other methods, due to the small number of studies included, that renders most methods inappropriate (Borenstein et al., 2009).All statistical analyses were conducted using the software STATA version 14.

The studies that reported differences in management of HTN among patients with schizophrenia and BPD were very heterogeneous in design and no meta-analysis could be conducted either. Therefore, a narrative summary of these results is also presented.

3. Results

The electronic search produced 19787 references. A total of ten studies published between 2006 and 2016, reporting on the risk of HTN, or differences in its management, among patients with schizophrenia or BPD met the inclusion criteria and were included in the review. Details of references identified in every stage of the search are presented in Fig. 1. All the studies had a large sample size, reliable measures of exposures and outcomes, long follow up, robust analyses and rigorous methods to minimize sampling error, bias, and confounding. The score in the quality assessment tool was ≥ 10/14 in all of them, and they were all considered to be of good methodological quality, and relevant for the question being raised in this review (National Institute of Health, 2016) (Supplement 2).

Five studies estimated the associations between BPD or schizophrenia and risk of HTN. Four studies compared the risk of HTN in patients with and without BPD (Stein et al., 2014; Perez-Pinar et al., 2016; Johannessen et al., 2006; Chien et al., 2013) and two of them additionally compared the risk of HTN for those with and without schizophrenia (Perez-Pinar et al., 2016; Johannessen et al., 2006). Finally, one study compared risk of HTN for patients with and without

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