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.

Key words: Hypertension, Bipolar disorder, schizophrenia, healthcare disparities, systematic review

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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 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.

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 criteria:

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; Sedgwick, 2012b) 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.

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 figure one. 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 schizophrenia only.(Crump et al., 2013) Table one shows the characteristics of these studies. They had been conducted in America, Asia and Europe. All studies were population based, their sample size ranged from 98714 to 6097834 and follow up lasted between five and 25 years. Only two of the studies that estimated risk of HTN for patients with BPD reported a significant association.(Johannessen et al., 2006; Chien et al., 2013) In four studies, routinely recorded clinical diagnoses of BPD or Schizophrenia and HTN, collected in a single country, were used (Johannessen et al., 2006; Chien et al., 2013; Perez-Pinar et al., 2016; Crump et al., 2013) However, in one study the WHO Composite International Diagnostic Interview was used to assess BPD in participants from 19 countries, who were also asked if, and when, had they been diagnosed of HTN.(Stein et al., 2014) This study had a large sample size but it was smaller than in others, which resulted in an estimate with a larger confidence interval. Given the methodological differences between the study by Stein et al(Stein et al., 2014) and the other three studies on BPD patients, it was decided not to include this study in the primary pooled estimate for risk of HTN, and include it in a sensitivity analysis.

The pooled Incidence Rate Ratio (IRR) of HTN for patients with BPD across the studies considered primarily, was 1.27 (95% CI: 1.15-1.40) (Figure 2). The heterogeneity between studies was not significant, I-squared = 32.6%, p=0.227. The inclusion of the study by Stein et al, attenuated the pooled estimate slightly and introduced substantial heterogeneity. However, the association remained significant, IRR of HTN for patients with BPD was, 1.19 (95% CI: 1.01-1.37) I-squared = 71.4%, p=0.015 (Supplement three).(Stein et al., 2014)

Only one of the three studies that estimated the risk of HTN for patients with schizophrenia reported a significant association; HR: 1.17 (1.05-1.29) p=0.003.(Perez-Pinar et al., 2016) Another one reported that the risk of HTN was significantly lower for women with Schizophrenia, but not significantly different for men.(Crump et al, 2013) The last one reported no significant association between schizophrenia and HTN.(Johannessen et al., 2006) The pooled IRR, was 0.94 (0.75 – 1.14), not significant, while the heterogeneity was substantial, 90.7%, p <0.001 (Supplement four). This heterogeneity could be explained by the different country and age of participants and the different results reported across studies. The exclusion of any of the studies, did not reduce the heterogeneity by more than 5%.

Five studies compared the management of HTN for patients with and without schizophrenia, and two studies for those with and without BPD. The characteristics of these studies are presented in table two. They had been conducted in America, Asia, and Europe. The sample size ranged from 485 to 2454844 and the follow up was between 1 and 35 years. All studies used clinical records but in two of them datasets were completed with epidemiological surveys.(Lahti et al., 2012; Laursen et al., 2014) One study only included patients with HTN at baseline.(Kim et al., 2010) One study reported that schizophrenia patients were approximately half as likely to have their blood pressure recorded.(Roberts et al., 2007) Another one found that patients with schizophrenia or BPD had lower prescription rate of angiotensin-converting-enzyme inhibitors, or angiotensin receptor blockers, but higher use of diuretics.(Laursen et al., 2014) Another study found that patients with schizophrenia had lower rate of prescription of antihypertensive medication.(Lahti et al., 2012) With regards to adherence to HTN medication, one study reported it to be lower for patients with schizophrenia or BPD (Kim et al., 2010) and another one found no association between schizophrenia and adherence.(Owen-Smith et al., 2016)

Discussion

A limited number of studies of good quality have investigated the risk of developing HTN for patients diagnosed with BPD or schizophrenia. The results of the meta-analyses suggest that the risk of HTN is increased by 27% (15% to 40%) for those with BPD, while it does not appear to be an increased for those with schizophrenia. The differences in the clinical care of HTN for patients with and without BPD or schizophrenia, have been studied in a small number of papers that observed very different outcomes. However, the evidence presented in these studies suggests that patients with schizophrenia or BPD have poorer care of HTN than people without these conditions.

To our knowledge this is the first systematic review that observes the risk of developing HTN among BPD and schizophrenia patients. The comprehensive search and critical assessment of studies conducted for this review allows for the estimation of the associations between BPD, schizophrenia and HTN obtained on a large number of patients. However, the reduced number of available studies represents a limitation of this paper. This may be consequence of publication bias as studies reporting not significant associations are less likely to be published.(Chapman et al., 2009) Some tools to assess the quality of systematic reviews require the presentation of a list of excluded studies, which is not presented in this paper.(AMSTAR 2007) The MOOSE criteria were used to undertake this review and meta-analysis, which, for accuracy and conciseness, recommends reporting only the number of full texts assessed and excluded. The MOOSE criteria is proposed in this type of studies by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network, and is widely used by systematic reviewers.(Stroup et al., 2000) Even though it was not made publically available, a protocol for this review, designed by the authors before the study was conducted, was followed. The different approach of clinicians

to patients with psychiatric conditions may have resulted in poorer recording of blood pressure in patients with schizophrenia and BPD.(Viron and Stern, 2010) This may have led previous studies, (Johannessen et al., 2006) and this review, to underestimate the risk of HTN for patients with schizophrenia and BPD.

The medication that patients with schizophrenia or BPD take may affect the risk of developing HTN. The pharmacological effect of different antidepressants and antipsychotics on HTN has been observed in other studies.(Correll et al., 2015; Liao et al., 2011) The positive effect of drugs in the mental health of these patients may also result in some of them adopting a healthier lifestyle, having better access to health services, and subsequently reducing the risk of HTN. Another factor that may be involved in the risk of HTN for those with schizophrenia and BPD is the high level of sedentary behavior observed in these patients.(Stubbs et al., 2016a; Vancampfort et al., 2016) The disruptions of neuroregulatory and neuroendocrine systems may also play a role on the association between severe mental illness and HTN.(Nousen et al., 2013; Poulter et al., 2015) However, this review did not analyse the role of potential explanatory factors, such as medication, for the associations between BPD or schizophrenia and HTN. This may be a limitation of this paper and also an area to be addressed by future studies. The mechanisms for the association between severe mental illness and HTN are still not well understood partly because the pathophysiology of HTN is largely unknown.(Poulter et al., 2015) The not significant association between schizophrenia and HTN, that we have observed in this review, is consistent with a recent systematic review of cross-sectional studies that reported that the pooled prevalence of HTN was increased for those with severe mental illness, but this difference was not statistically significant.(Vancampfort et al., 2015b)

Many factors affect the healthcare of patients with BPD and schizophrenia. These include some symptoms of the mental health condition such as memory impairment or reduce motivation, issues related to the health service, for example the difficulties to book an appointment with the doctor, and also wrong beliefs from the clinicians about these patients, such as the underestimation of them as capable partners in their own care.(Viron and Stern, 2010) A good coordination between all clinicians from primary and secondary care is essential to avoid gaps in care that can result in undetected or poorly controlled HTN.

Clinicians should be aware that patients with BPD have a higher risk of developing HTN, and that the healthcare for it is worse among those with BPD or schizophrenia. A good understanding of the risk of HTN among people with schizophrenia or BPD is particularly relevant, since it has been observed that these patients have an increased prevalence of other CV risk factors that can interact with HTN and result in worse CV health.(de Leon and Diaz, 2005; Stubbs et al., 2015; Stubbs et al., 2016b; Vancampfort et al., 2015a; Vancampfort et al., 2015b; Wilens et al., 2016) Special clinical attention is required, to achieve a good control of all CV risk factors in this vulnerable population which could eventually lead to a life expectancy similar to the one of people without psychiatric conditions.

More prospective studies estimating the association and mechanisms of HTN among patients with BPD or schizophrenia are required. Further studies are also needed to understand the main points where the health care inequalities happen for those with schizophrenia or BPD. Studies on health care inequalities could consider comparing differences in outcomes defined by guidelines as the main steps of HTN care (screening, diagnosis, treatment, follow up and control).(National Institute of Health and Cae Execellence 2016) All these studies would provide stronger evidence on risk of HTN, and the areas of poor healthcare, and could inform innovative interventions to

improve the CV care and ultimately reduce the CV morbidity and overall mortality of patients with BPD or schizophrenia.

Author / Year (Country)	N	Follow up	Female %	Age	Exposure	Association	Comments
Johannessen 2006 (Denmark)	139037	25 y	NR	≥15	Schiz. BPD	IRR: 0.93 (0.77-1.14) p<0.51 IRR:1.27 (1.16-1.39) p<0.001	Nationwide data from various administrative health service registers
Chien 2013 (Taiwan)	766427	5 y	NR	≥18	BPD	RR: 1.40 (1.20–1.62) p<0.001	Data from the National Health Research Institute
Crump 2013 (Sweden)	6097834	7y	51	≥25	Schiz	Women: 0.78 (0.69–0.89) Men: 0.84 (0.76–0.94)	Data from all persons who had lived in Sweden for ≥ 2 years at start of follow up
Stein 2014 (Colombia Mexico Peru USA China Iraq Israel Japan Belgium France Germany Italy Netherlands Poland UK Portugal Romania Spain N.Zealand)	98714	NR	NR	≥18	BPD	OR: 0.9 (0.7-1.2)	Data from the World Mental Health Survey
Pérez-Piñar 2016 (UK)	524952	10 y	47	≥30	Schiz. BPD	HR:1.17 (1.05-1.29) p=0.003 HR: 1.12 (0.90-1.39) p=0.298	Data from Primary Care Records from 140 London practices

Table 1. Characteristics of studies reporting risk of hypertension

Y: years; NR: Not reported; Sciz: Schizophrenia; BPD: Bipolar disorders; IRR: Incidence rate ratio; RR: relative risk; OR: odds ratio, HR: hazard ratio.

	N	Follow up	Female %	Age	Exposure	Outcome	Association	Comments
Roberts 2007 (UK)	485	3y	NR	21-64	Schiz.	BP recorded	OR: 0.43 p<0.01	Data from Primary Care Records from 22Birmingham (UK) practices.
Kim 2010 (South Korea)	2454844	1y	58	>20	Schiz. BPD	Adherence to HTN treatment (CMA)	Schiz OR: 0.746 (0.628–0.886) BPD OR: 0.793 (0.644–0.977)	Data the National Health Insurance, which covers the whole country.
Lahti 2012 (Finland)	10915	35y	47	≥35	Schiz.	HTN treatment	HR: 0.37 (0.22–0.61) p<0.001	Data from the National Social Insurance of People on Medication for Chronic Disease
Laursen 2014 (Denmark)	1061532	11y	NR	≥10	Schiz. BPD	CV drugs use	Schiz: lower use of ACEI/ARB, CCB and beta blockers Higher use of diuretics BPD: lower use of ACEI/ARB. Higher use of diuretics.	Data from Nationwide data from various administrative health service registers and the Helsinki Birth Cohort Study
Owen-Smith 2016 (USA)	1420	1y	56	18-70	Schiz.	Adherence to ACEI/ARB (MPR)	OR: 0.98 (0.72-1.33)	Data from medical records of 13 Mental Health Research Network sites

Table 2. Characteristics of studies comparing management of HTN in patients with and without mental health disorders.

Y: year; Schiz: Schizophrenia; BPD: Bipolar disorder ; CMA: cumulative medication adherence scale; ACEI: Angiotensin converting Enzyme Inhibitors; ARB: Angiotensin receptors blockers; CCB: Calcium channel blockers; MPR: Medication Possession Ratio

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