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Relative risks of cardiovascular disease in people prescribed olanzapine, risperidone and quetiapine

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ABSTRACT

Antipsychotics may confer long term benefits and risks, including cardiovascular disease (CVD) risk. Several studies using routine clinical data have reported associations between antipsychotics and CVD but potential confounding factors and unclear classification of drug exposure limits their interpretation.

Method: We used data from The Health Improvement Network, a large UK primary care database to determine relative risks of (CVD) comparing similar groups of people *only* prescribed olanzapine versus either risperidone or quetiapine. We included participants over 18 between 1995 and 2011. To assess confounding factors we created propensity scores for being prescribed each antipsychotic. We used propensity score matching and Poisson regression to calculate the CVD incidence rate ratios for olanzapine versus the other two drugs.

Results: We identified 18,319 people who received a single antipsychotic during follow-up ($n = 5090$ risperidone, 7797 olanzapine and 4613 quetiapine). In unmatched analyses, the CVD incidence rate ratio (IRR) for olanzapine versus risperidone was 0.63 (0.51–0.77) but the propensity score matched IRR was 0.78 (0.61–1.02). In the unmatched olanzapine versus quetiapine analysis the IRR adjusted for age and sex for olanzapine was 1.52 (1.16–1.98) but the propensity score matched analysis gave an IRR of 1.08 (0.79–1.46).

Conclusions: After propensity score matching, we found no statistical differences in CVD incidence between olanzapine and either risperidone or quetiapine. Analyses which did not account for confounding factors produced very different results. Researchers must address confounding factors when designing observational studies to assess adverse outcomes of drugs, including antipsychotics.

1. Introduction

Cardiovascular disease (CVD) mortality and morbidity is markedly elevated in people with severe mental illnesses such as schizophrenia, for reasons including smoking, deprivation and health care (Osborn et al., 2007). The contribution of antipsychotic medication to CVD risk and CVD mortality has generated scientific, clinical and policy-focused debate. The mechanism might include the cumulative adverse effects of different agents, including weight gain, glucose, ECG abnormalities and lipid levels. A systematic review in 2009 concluded that antipsychotics were associated with increased CVD mortality in schizophrenia (Weinmann et al., 2009). However contradictory evidence has emerged in the past five years. Large cohort studies have been published using linked national data in Finland (Kiviniemi et al., 2013; Tiihonen et al., 2009), Sweden (Torniainen et al., 2015, Crump et al., 2013) of people with long term or first onset schizophrenia as well as UK studies including all people using antipsychotics in primary care (Murray-Thomas et al., 2013). These studies have shown varying results, reporting that second generation antipsychotic users are either more or less likely to develop from cardiovascular disease. There has been particular concern regarding olanzapine in terms of cardiovascular risks, including weight gain, and it is one of the most commonly prescribed antipsychotics in the UK and internationally (Weinmann et al., 2009, Marston et al., 2014).

Comparing the risk for CVD with individual antipsychotics such as olanzapine is methodologically challenging; it requires large studies with sufficient person years of follow-up. Most studies addressing these questions use large routinely collected data sources, since bespoke trials and cohort studies of this size and length of follow-up are probably unfeasible. However using routine data bring major challenges. This includes the highly heterogeneous groups of people in the data source, often deriving from quite different time periods. More historical cohorts

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may have poorer quality information on older exposures, but they often have greater statistical power by virtue of larger numbers of CVD events. More contemporary cohorts of younger people may provide higher quality data on exposures (such as smoking or drug dose), but will have fewer CVD events. The theoretical pathway by which antipsychotics may predispose to CVD is probably complex and lengthy. Different agents may affect different parts of this pathway. These effects cannot be differentiated unless we select "purer" cohorts exposed to single antipsychotic agents during follow-up. However in real life clinical setting, from which data are often derived, patients switch between medications, stopping and starting medications for periods of time (Lieberman et al., 2005). This makes it difficult to establish which agent might be associated with any elevated or decreased risk of CVD mortality. It is also important to carefully select outcomes in research using routine databases. Many studies of antipsychotic outcomes simply combine all causes of mortality however this approach is unlikely to yield meaningful evidence when the mechanisms underlying different diseases and causes of death (such as suicide and CVD) are so varied (Weinmann et al., 2009; De Hert et al., 2010).

A further challenge with routine data is assessing the role of confounding factors, when estimating the relationship between different antipsychotics and CVD. To do this we need good quality data on potential confounding factors such as co-morbid physical health, diagnoses, or substance misuse. These variables are not available in many large observational datasets.

We designed a study to compare risk of incident CVD in people prescribed the three most commonly used antipsychotic agents in the UK, olanzapine, risperidone and quetiapine. We aimed to address some of the aforementioned challenges when using routinely available clinical data. We aimed to select groups of people with who only used one of the three most common antipsychotics during their follow-up and to compare their risk of incident CVD. We assessed whether olanzapine confers greater risk of CVD than other second generation antipsychotics. We used propensity score matching to select three groups of antipsychotic users who were similar in terms of their balance of known confounders.

2. Methods

2.1. Study design

A prospective cohort study using routinely collected data in UK primary care.

2.2. Setting

We extracted data from The Health Improvement Network (THIN) (The Health Improvement Network, 2014), a United Kingdom primary care database which derives data from routine administrative and clinical practice. We used data from an established cohort of THIN patients prescribed first and second generation antipsychotics in UK primary care (Marston et al., 2014). THIN includes longitudinal data from more than 12 million patients with a geographical spread that is generally representative of the UK general population (Blak et al., 2011). Staff at general practices enter data using a hierarchical system of Read codes (Chisholm, 1990; Dave and Petersen, 2009), for information such as symptoms, signs and diagnoses. THIN has been successfully used for a range of mental health and pharmaco-epidemiological research including work regarding antipsychotics, severe mental illnesses and cardiovascular disease (Marston et al., 2014; Hayes et al., 2016; Osborn et al., 2014).

2.3. Participants

The cohort included all people aged over 18 with an electronic record of being prescribed olanzapine, risperidone or quetiapine during follow-up, between 1995 and December 2011.

We excluded people with pre-existing cardiovascular disease, heart failure or dementia.

2.4. Main exposure

Since we aimed to identify sole users of the most common three antipsychotics, we excluded people who were prescribed additional first or second antipsychotics during follow-up, in addition to their index drug. This derived three groups of people solely receiving 1) olanzapine 2) risperidone or 3) quetiapine.

2.5. Follow-up period

Follow up commenced at first prescription of risperidone, olanzapine or quetiapine and ended at death, incident CVD, the patient leaving the practice or December 2011. We excluded those with less than 6 months follow-up data.

2.6. Covariates for propensity score matching

In order to balance the observed characteristics of the groups receiving the different antipsychotics, we generated propensity scores for receiving olanzapine, versus either risperidone or quetiapine. We created plots of propensity score distributions to visually compare 1) olanzapine versus risperidone sole users and 2) olanzapine versus quetiapine sole users. We then used propensity score matching to select groups of patients receiving the pairs of drugs of interest. We included people whose propensity scores overlapped using predefined criteria below and we excluded patients for whom we could not find an eligible comparison. We selected patients using 1:1 matching of propensity score, without replacement, but including individuals with tied scores. Calipers for matching pairs of patients were set at 0.2 of a standard deviation of the propensity score as recommended by Austin (2011) for observational studies.

We calculated the propensity scores for each patient using logistic regression. We included a range of relevant variables in the model. These variables were selected by the research team, including epidemiologists, experts in primary care data, academic GPs and psychiatrists. We were deliberately inclusive and made use of any socio-demographic, biometric, diagnostic or co-prescribing variable which might plausibly influence or be related to the choice of olanzapine risperidone quetiapine or which might influence the CVD outcome.

We included the following variables: Mental health diagnoses (category of Severe Mental Illness diagnosis, namely schizophrenia, bipolar disorder or other psychosis (Hardoon et al., 2013)), ADHD, anxiety, depression, OCD, personality disorder, post-traumatic stress disorder, sleep disorders (Marston et al., 2014); chronic physical illnesses at any time (defined as asthma, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, hypothyroid, learning disability, on the palliative care register); receipt of other main classes of medication at any time (antidepressants, diabetes medication, anti-hypertensive medication at any time, hypnotics, insulin, statin use); socio-demographic factors and health indicators at any time before baseline, using the value closest to baseline where there was more than one measurement. These included age at baseline, sex, Townsend quintile (The Townsend index, a widely used measure of geographical social deprivation; Townsend et al., 1986), time period when the person entered the cohort, high alcohol intake, illicit drug use, ethnicity, smoking status, number of drug subchapters from the BNF prescribed from taken in the year before baseline, systolic blood pressure, height, weight, blood glucose, HbA1c, HDL cholesterol, total cholesterol); mental health consultations (a record of seeing a psychologist, a psychiatrist, or mental health crisis). These definitions have previously been published (Marston et al., 2014; Osborn et al., 2014).

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