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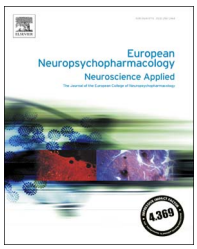

Comparative risk of death in older adults treated with antipsychotics: A population-based cohort study

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Abstract
Although the use of antipsychotics has been associated with an increased risk of death, data on the safety of individual substances is scarce. We thus aimed to compare the risk of death in new users of individual antipsychotics aged =>65 years and conducted a cohort study in the German Pharmacoepidemiological Research Database between 2005 and 2011. Patients were followed from initiation of treatment until death, 90 days after cohort entry, end of insurance or the end of the study period. Multivariable cox regression was used to estimate confounder adjusted hazard ratios (aHR) of death for 14 individual antipsychotics compared to risperidone. In sensitivity analyses, we also applied high-dimensional propensity score (HDPS) methods to explore possible unmeasured confounding. In a cohort of 137,713 new users of antipsychotics, a higher risk of death was found for haloperidol (aHR: 1.45; 95% confidence interval: 1.35–1.55), levomepromazine (aHR: 1.34; 1.16–1.54), zuclopenthixol (aHR: 1.32; 1.02–1.72) and to a lesser extent for melperone (aHR: 1.13; 1.07–1.19) compared to risperidone. Lower risks were observed for quetiapine, prothipendyl, olanzapine, tiapride, clozapine, perazine and flupentixol. In subgroup analyses, levomepromazine and chlorprothixene were only associated with a higher risk of death in patients aged =>80 years and with dementia. The application of HDPS methods did not substantially change the results. In conclusion, our study suggests that

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initiation of haloperidol, levomepromazine, zuclopenthixol and chlorprothixene treatment is associated with an increased risk of death compared to risperidone and should be avoided in older patients except in palliative care when treatment alternatives are available.

1. Introduction

Antipsychotics are mostly used for severe psychotic disorders, e.g. schizophrenia, manic episodes of bipolar disorders and major depression with psychoses (Glick et al., 2001). In older adults, they are also commonly prescribed in psychoses related to Parkinson's disease, anxiety disorders or insomnia (McKean and Monasterio, 2015) and particularly for the treatment of behavioural and psychological symptoms of dementia (BPSD) such as aggression, agitation, and psychomotor restlessness (Liperoti et al., 2008). For instance, approximately 25 percent of patients aged 65 years and older with a new diagnosis of dementia are treated with an antipsychotic in Germany (Schulze et al., 2013), even though strong concerns have been raised regarding their use in this subgroup. Meta-analyses of randomised placebo-controlled trials have only shown modest efficacy for some antipsychotics in older patients with dementia (Maher et al., 2011; Tan et al., 2015) and their use has been associated with severe adverse drug reactions resulting in substantial premature death (Maust et al., 2015; Trifiro et al., 2014). Consequently, regulatory agencies in Europe and the United States issued warnings about the increased risk of death when using antipsychotics in older patients (European Medicines Agency (EMA), 2008; U.S. Food and Drug Administration (FDA), 2008) and recommended to avoid their use in patients with dementia unless non-pharmacological treatment has failed or the patient is a threat to himself or others (American Geriatrics Society Beers Criteria Update Expert Panel, 2012; Livingston et al., 2014; National Institute for Health and Clinical Excellence (NICE), 2007).

So far, several observational studies compared the safety of conventional and atypical antipsychotics, but most of them did not include an analysis of individual substances (Luijendijk et al., 2016; Trifiro et al., 2014). Moreover, two studies from the Unites States analysed the mortality risk in new users of olanzapine, quetiapine, haloperidol, aripiprazole and ziprasidone compared to risperidone in nursing home residents (Huybrechts et al., 2012) and community-dwelling older adults (Gerhard et al., 2014). Both studies found a higher mortality risk for patients beginning therapy with haloperidol and a potentially lower risk for those starting quetiapine (Gerhard et al., 2014; Huybrechts et al., 2012). In another study from Denmark (Sahlberg et al., 2015), these findings were replicated and extended to further individual antipsychotics; however, patients with cancer and patients receiving palliative care were not excluded leading to a possible overestimation of the mortality risk for conventional antipsychotic agents used in patients with terminal illness (Luijendijk et al., 2016).

In general, antipsychotics that are a frequently used in other countries, e.g. melperone, pipamperone, zuclopenthixol, clozapine, tiapride and amisulpiride, have not yet been analysed. Therefore, the aim of our study was to compare the risk of death in older adults without cancer and not receiving palliative care who started treatment with individual antipsychotics in Germany.

2. Experimental procedures

2.1. Data Source

Data for this study was retrieved from the German Pharmacoepidemiological Research Database (GePaRD). GePaRD consists of claims data from four German statutory health insurance providers (SHIs) covering about 20 million insured members throughout Germany. This reflects approximately 25% of the whole German population. Acceptability of German claims data for pharmacoepidemiological research has been assessed methodologically as well as by validation studies based on GePaRD (Garbe et al., 2011; Ohlmeier et al., 2015; Pigeot and Ahrens, 2008). More recently, GePaRD has been used for various types of pharmacoepidemiological studies including drug utilisation studies and studies investigating the risks of drugs or vaccines (Jobski et al., 2011, 2014; Mikolajczyk et al., 2015; Schink et al., 2014).

The database comprises core data, hospital data, outpatient dispensing data and outpatient medical care data of all SHI members who have been enroled in one of the four SHIs since 2004. Core data contain information on sex, year of birth, insurance status, and reason for deregistration from the SHI. Hospital data comprise the date of admission and discharge, different types of diagnoses including the admission, main discharge, secondary and ancillary diagnoses as well as diagnostic and therapeutic procedures, and the reason for hospital discharge including death. Outpatient medical care data incorporate diagnoses on a quarterly basis with their diagnostic certainty (confirmed, suspected, excluded, and status post), and types and dates of outpatient diagnostic and therapeutic procedures. All diagnoses in GePaRD are coded according to the German Modification of the 10th revision of the International Classification of Diseases (ICD-10GM). Dispensation data contain information on prescriptions dispensed in a pharmacy and reimbursed by the respective SHI. Drugs purchased over the counter and in-hospital medication are not covered in GePaRD with few exceptions. Dispensation information also includes the dates of the prescription and dispensation, the number of prescribed packages, and the central pharmaceutical number of the drug. Based on a central pharmaceutical reference database, information on the generic and brand name of the drug, packaging size, strength, defined daily dose (DDD), and other pharmaceutical information can be linked to GePaRD.

In Germany, the utilisation of health insurance data for scientific research is regulated by the Code of Social Law. All SHIs providing data as well as the federal and regional authorities approved the use of the data for this study. Informed consent was not required by law, since the study was based on pseudonymous data.

2.2. Study population and design

We conducted a cohort study comprising all new users of antipsychotics in GePaRD aged 65 years and older between January 1,

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