Psychiatry Research 265 (2018) 82–86

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

All-cause mortality in older adults with affective disorders and dementia under treatment with antipsychotic drugs: A matched-cohort study

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ARTICLE INFO

Keywords:
Antipsychotic agents
Mental health
Cohort study
Pharmacoepidemiology
Older adults

ABSTRACT

We aimed to compare the mortality risk between patients with affective disorders and dementia under treatment with antipsychotics. To do this, a matched-cohort study based on an electronic database of a tertiary teaching hospital in Argentina was performed. Antipsychotic exposure was defined as any antipsychotic drug initiated by the patient. Primary outcome was defined as all-cause mortality during the 5-year follow-up period. To estimate the association between baseline diagnosis (affective disorders vs. dementia) and all-cause mortality, we used a multivariate generalized linear model with robust standard errors. Of 1008 eligible patients, 114 age-matched pairs were included in the present study. The primary event occurred in 23 patients (20%) and 17 patients (15%) in the dementia and affective disorder group respectively. In the adjusted model, the risk of all cause mortality for the affective disorders group was 0.92 times the risk for the dementia group (95%CI, 0.54–1.59, $p = 0.77$). In conclusion, older patients with affective disorders starting antipsychotic treatment presented with a similar risk of all-cause mortality during the 5-year follow-up when compared to older patients with dementia who were also initiating either typical or atypical antipsychotic medications. Closer medical attention to older patients with mental conditions under antipsychotic treatment remains warranted.

1. Introduction

The use of antipsychotic drugs in the treatment of behavioral disturbances that are typically associated with dementia - such as psychosis, agitation, aggression, irritability, and disinhibition - has raised serious concerns regarding the safety of such therapeutic strategy. In 2005, the FDA issued a warning stating that atypical antipsychotics drugs were associated with increased mortality in comparison with placebo in people with dementia (FDA, 2005). In 2008, a similar black-box warning was issued for conventional antipsychotic drugs (FDA, 2010). In general, the increased mortality risk associated with both typical and atypical antipsychotics may be attributed to either infections, arrhythmia or cardiovascular disease (Kuehn, 2005). Furthermore, recent reports have also shown similar results among older adults with other conditions such as Parkinson's disease or stroke under antipsychotic treatment (Frandsen et al., 2014; Jennum et al., 2016).

However, evidence regarding this matter in psychiatric disorders remains both scarce and contradictory. For example, antipsychotic treatment might explain the excess mortality risk observed in patients with schizophrenia (SZ) (Daumit et al., 2008; Goff et al., 2005; Laursen et al., 2014; Raedler, 2010; Saha et al., 2007). Conversely, the FIN-11 study (Tiihonen et al., 2009) did not show an increase in mortality risk when second generation antipsychotic drugs were introduced. Specifically, regarding older adults with Mood Disorders (MD), there is a conspicuous dearth of studies exploring the effects of antipsychotic treatment on mortality. Nevertheless, a recent study has shown higher mortality rates when patients with Bipolar Disorder were receiving antipsychotics rather than anticonvulsants (Bhalerao et al., 2012). This topic remains of special interest since other therapeutic options (i.e., mood stabilizers or antidepressant agents) with proven efficacy are also available for the treatment of such conditions, which contrasts with the scenario in both dementia and SZ. Given that prescription of antipsychotic drugs in MD is rising (Kessing et al., 2016) - and most are using them on a long-term basis (Olfson et al., 2015) - further

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https://doi.org/10.1016/j.psychres.2018.04.034
Received 27 August 2017; Received in revised form 8 April 2018; Accepted 11 April 2018
Available online 19 April 2018
0165-1781/

clarification of the role of these drugs on mortality in patients with MD remains paramount.

Thus, our aim was to delineate the survival experience of older adults with MD starting antipsychotic treatment. For this purpose, we compared the overall mortality risk between patients with MD and dementia under treatment with antipsychotic drugs. We selected dementia patients as the reference group since it stands as the most-validated clinical population in which antipsychotic treatment increases mortality rates.

2. Methods

2.1. Data source and data extraction

The present study was a matched-cohort study based on an electronic database of a tertiary teaching hospital in Buenos Aires, Argentina. The institutional review board provided approval for this study. Health-plan electronic data includes drug prescriptions and its characteristics, including dispensing date, drug name, dose, quantity, and duration of supply - all of which have been shown to be reliable measures of drug treatment (Johnson and Vollmer, 1991; West et al., 1995). Moreover, it contains a fully integrated health-care database with both inpatient and outpatient information regarding baseline comorbidities, clinical outcomes and laboratory measures. We used these health records to gather baseline information on demographics, clinical history and comorbidities, physical examination, and laboratory and radiological data. We also used the registry to capture information on vital status during follow up. Finally, as patients belonging to the present health-plan receive their clinical attention through the tertiary Hospital, all medical care was captured by the present charts.

2.2. Study design and population

We selected 1,229 eligible patients starting antipsychotic treatment in an outpatient basis between January 1 2002 and December 31 2007 (Fig. 1). Patients (with either dementia or affective disorder) were matched by age (± 0.5 years) at the start of follow-up. We identified 114 age-matched pairs and thus, our cohort was comprised of 228 patients. Index date was defined as the calendar time for the first qualifying antipsychotic prescription (i.e., the first refill after the first supply ever received by the patient had ran out).

2.3. Exposure to antipsychotic treatment

Antipsychotic exposure was defined as any antipsychotic drug initiated by the patient with at least one extra expenditure within the first 3 months of prescription. Antipsychotics were divided into either typical (haloperidol, trifluoperazine, levomepromazine and thioridazine) or atypical (olanzapine, aripiprazole, risperidone, quetiapine and clozapine) medications.

Treatment discontinuation was defined by any period of more than, or equal to, 3 months without claiming the prescribed AP drug. In the case that a patient stopped their AP medication, an approximation to an intention-to-treat analysis was performed in which patients were followed until disenrollment, end of follow up or primary outcome regardless of discontinuation of index drug.

2.4. Covariates

Demographic variables including age, gender, and psychiatric diagnosis were recorded. Baseline characteristic regarding prior cardiovascular events (such as ischemic stroke, myocardial infarction, diagnosis of peripheral artery disease and atrial fibrillation) were included. Risk factors (e.g. gender, blood pressure, type 2 diabetes) and laboratory markers associated with cardiovascular disease (low density lipoprotein, high density lipoprotein, total triglycerides, and fasting plasma glucose) were also evaluated. In addition, prevalent chronic pulmonary obstructive disease, heart failure, chronic renal failure, HIV diagnosis, prior pulmonary thromboembolism, liver disease, malignancy and both tobacco and alcohol use were recorded. Finally, the number of hospitalizations during follow-up and number of suicide attempts were measured (Bodén et al., 2015; Gardette et al., 2012).

Regarding concomitant pharmacologic treatment, dispensing of non-AP drugs were also captured if the patient had a documented prescription by the time the AP drug was started. Non-AP drugs included cholesterol-lowering agents, antihypertensive medication, antithrombotic agents, lithium, anticonvulsants, benzodiazepines, antidepressants, cholinesterase inhibitors, corticosteroids, and anti-diabetic agents.

All covariates were measured within a 3-month period prior to or on the index date.

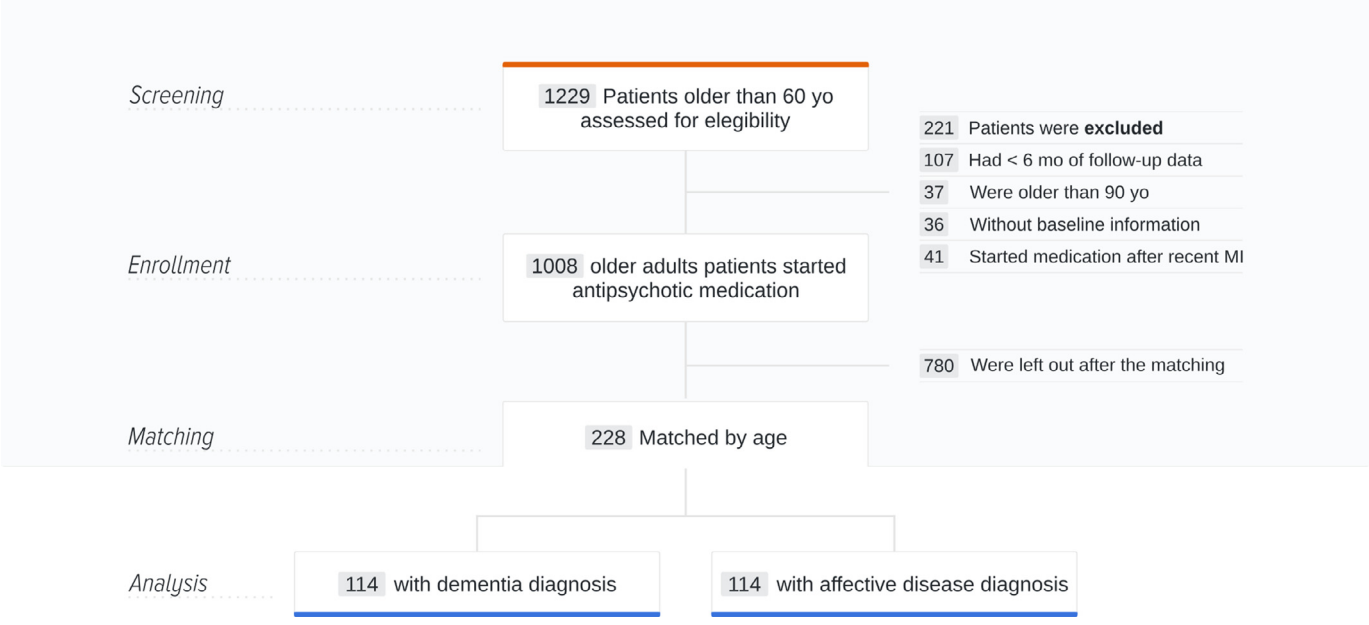

Fig. 1. Flowchart of patients.