European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro

Increased all-cause mortality with use of psychotropic medication in dementia patients and controls: A population-based register study

Poul Jennum[a,*], Lone Baandrup[b], Rikke Ibsen[c], Jakob Kjellberg[d]

[a]*Danish Center for Sleep Medicine, Clinic Clinical Neurophysiology, Faculty of Health Sciences, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark*
[b]*Center for Neuropsychiatric Schizophrenia Research & Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Center Glostrup, Copenhagen University Hospital, Glostrup, Denmark*
[c]*i2minds, Klosterport 4E, Aarhus, Denmark*
[d]*Danish National Institute for Local and Regional Government Research, Copenhagen, Denmark*

Received 9 November 2014; received in revised form 10 August 2015; accepted 15 August 2015

KEYWORDS
Dementia;
Hypnotics;
Antidepressants;
Antipsychotics;
Benzodiazepines;
All-cause mortality

Abstract
We aimed to evaluate all-cause mortality of middle-aged and elderly subjects diagnosed with dementia and treated with psychotropic drugs as compared with controls subjects.
Using data from the Danish National Patient Registry, n=26,821 adults with a diagnosis of dementia were included. They were compared with 44,286 control subjects with a minimum follow-up of four years and matched on age, gender, marital status, and community location. Information about psychotropic medication use (benzodiazepines, antidepressants, antipsychotics) was obtained from the Danish Medicinal Product Statistics.
All-cause mortality was higher in patients with dementia as compared to control subjects. Mortality hazard ratios were increased for subjects prescribed serotonergic antidepressant drugs (respectively, HR=1.355 (SD=0.023), P=0.001 in patients; HR=1.808 (0.033), P<0.001 in controls), tricyclic antidepressants (HR=1.004 (0.046), P=0.925; HR=1.406 (0.061), P<0.001), benzodiazepines (HR=1.131 (0.039), P=0.060); HR=1.362 (0.028), P<0.001), benzodiazepine-like drugs (HR=1.108 (0.031), P=0.078; HR=1.564 (0.037, P<0.001), first-generation antipsychotics (HR=1.183 (0.074), P=0.022; HR=2.026 (0.114), P<0.001), and second-generation antipsychotics (HR=1.380 (0.042), P<0.001; HR=1.785 (0.088), P<0.001), as compared with no drug use. Interaction analysis suggested statistically significantly higher

*Correspondence to: Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Center for Healthy Ageing, Faculty of Health Sciences, University of Copenhagen, Rigshospitalet, DK 2600 Glostrup, Denmark. Tel.: +45 38632512; fax: +45 43233933.
E-mail addresses: poul.joergen.jennum@glo.regionh.dk (P. Jennum), lone.baandrup@regionh.dk (L. Baandrup), rikke@i2minds.dk (R. Ibsen), jakj@kora.dk (J. Kjellberg).

http://dx.doi.org/10.1016/j.euroneuro.2015.08.014

Please cite this article as: Jennum, P., et al., Increased all-cause mortality with use of psychotropic medication in dementia patients and controls: A population-based register study. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.08.014

mortality hazard ratios for most classes of psychotropic drugs in controls than in dementia patients.

We found that use of psychotropic drugs is associated with increased all-cause mortality in both patients with dementia and control subjects. Thus, the frequently reported increased mortality with antipsychotic drugs in dementia is not restricted to subjects with impaired cognition and is not restricted to only one class of psychotropic drugs.

1. Introduction

Neurodegenerative diseases causing cognitive impairment, motor dysfunction, and social disability will affect more than a quarter of the ageing population. Catching dementia has deleterious effects on social function, employment, quality of life, and relation to family, partner, and peers. The most common types of dementia are Alzheimer's and vascular dementias, Parkinsonian dementia, and other or mixed causes. Apart from the progressive cognitive deficits, motor symptoms, and social decline, a significant number of patients suffer from a range of neuropsychiatric symptoms like comorbid insomnia, sleep fragmentation, daytime somnolence, circadian disturbances, sundowning, depressed mood, agitation, aggression, disturbed behaviour, and psychotic symptoms (hallucinations and delusions) (Liperoti et al., 2008). Thus, considerable rates of patients with dementia are treated with various psychotropic medications despite reports of limited efficacy (Ballard et al., 2008).

In recent years, concern has been raised about increasing use of psychotropic drugs including off-label use, tolerability and safety profile (Kripke et al., 1998; Rintoul et al., 2013; Merlo et al., 2000). Studies of large groups of patients with chronic insomnia have raised concerns about increased mortality rates in benzodiazepine-treated patients, especially when used in combination with other psychotropic drugs (Kripke et al., 2012; Kripke, 2009; Mallon et al., 2009). Furthermore, use of benzodiazepines has been associated with aggravation of cognitive impairment in Alzheimer patients and a potential risk of worsening or developing Alzheimer's disease in otherwise healthy subjects (Montastruc et al., 2013; Lauterbach, 2013; Rosenberg et al., 2012; Vigen et al., 2011; Wu et al., 2009). Patients with dementia suffer from a range of comorbid diseases and potentially sleep disordered breathing, and thus respiratory depressants should only be cautiously used. Furthermore, comorbid cardiac and other somatic diseases may potentially increase the risk of psychotropic drug treatment when side effects involve such functions. A number of observations have reported an excess mortality in patients with Alzheimer's disease treated with antipsychotic drugs (Kales et al., 2007;Kryzhanovskaya et al., 2006;Wilson et al., 2006; Wang et al., 2005; Schneider et al., 2005;Factor et al., 2003; Czekalla et al., 2001), but there is a lack of observations in patients with dementia using hypnotics or antidepressants, in particular combinations of psychotropic drugs. Critique of the existing studies has been raised due to poor methodology, including a lack of control group (Pratt et al., 2012). Thus, it is insufficiently investigated if the excess mortality associated with antipsychotic drug use is constricted to dementia patients or is a more general effect, and whether use of other psychotropic drugs is associated with mortality.

The aim of this study was to evaluate the association of psychotropic drug use with all-cause mortality in dementia patients and control subjects.

2. Experimental procedures

2.1. Subjects

The method used for this study was previously described in detail elsewhere (Jennum et al., 2013a, 2013b, 2013c). In brief, in Denmark all public and private hospital contacts are recorded in the National Patient Registry (NPR) with respect to the time of the contact and information about primary and secondary diagnoses. The NPR includes administrative information and details of all diagnoses, diagnostic methods, treatment procedures, hospitalisations, and outpatient services. These data are recorded using the *International Classification of Diseases, 10th Revision (ICD-10)*. Patients are diagnosed with dementia in the NPR only after adequate examination in an inpatient or outpatient specialized setting.

Using the NPR, we identified all subjects with a diagnosis of dementia between 1997 and 2009 as defined by the following ICD-10 codes: F00 (Alzheimer's disease), F01 (vascular dementia), F02 (Pick's disease, dementias associated with Creutzfeldt-Jakob's disease, and dementias associated with Huntington's chorea, Parkinson's disease and HIV), and F03 (non-classified dementias). Because the NPR is a population-based database, the data we extracted included all Danish citizens with a dementia diagnosis (subjects with other comorbid diagnoses were not excluded from the population). As data were available for the entire observation period, we were able to trace patients retrospectively and prospectively, relative to the time of their diagnosis. Subsequently, using data from Denmark's Civil Registration System Statistics, we randomly selected citizens of the same age, gender, county of residence, and marital status as the patients but who did not have a diagnosis of dementia. Parity of socio-economic status (SES) was ensured by selecting control subjects from the same part of the country in which the patients lived and by matching for partnership (including marital status). The ratio of control subjects to patients was 2:1 in order to account for variation among the controls. Patients and matched control subjects that could not be identified in the Coherent Social Statistics database were excluded from the sample. The patients and matched control subjects were traced retrospectively and prospectively for up to 12

Please cite this article as: Jennum, P., et al., Increased all-cause mortality with use of psychotropic medication in dementia patients and controls: A population-based register study. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.08.014