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Research paper

Potentially inappropriate medication: Association between the use of antidepressant drugs and the subsequent risk for dementia

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ABSTRACT

Background: Potentially inappropriate medication (PIM) is associated with an increased risk for detrimental health outcomes in elderly patients. Some antidepressant drugs are considered as PIM, but previous research on the association between antidepressants and subsequent dementia has been inconclusive. Therefore, we investigated whether the intake of antidepressants, particularly of those considered as PIM according to the Priscus list, would predict incident dementia.

Methods: We used data of a prospective cohort study of non-demented primary care patients (n = 3239, mean age = 79.62) to compute Cox proportional hazards models. The risk for subsequent dementia was estimated over eight follow-ups up to 12 years depending on antidepressant intake and covariates.

Results: The intake of antidepressants was associated with an increased risk for subsequent dementia (HR = 1.53, 95% CI: 1.16–2.02, p = .003; age-, sex-, education-adjusted). PIM antidepressants (HR = 1.49, 95% CI: 1.06–2.10, p = .021), but not other antidepressants (HR = 1.04, 95% CI: 0.66–1.66, p = .863), were associated with an increased risk for subsequent dementia (in age-, sex-, education-, and depressive symptoms adjusted models). Significant associations disappeared after global cognition at baseline was controlled for.

Limitations: Methodological limitations such as selection biases and self-reported drug assessments might have influenced the results.

Conclusions: Only antidepressants considered as PIM were associated with an increased subsequent dementia risk. Anticholinergic effects might explain this relationship. The association disappeared after the statistical control for global cognition at baseline. Nonetheless, physicians should avoid the prescription of PIM antidepressants in elderly patients whenever possible.

1. Introduction

Potentially inappropriate medication (PIM) is associated with an increased risk for adverse drug effects in elderly patients, with an increased risk for detrimental outcomes such as hospitalization and mortality (e.g., Lau et al., 2005), and with higher monetary costs due to

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hospital admissions caused by adverse drug events (e.g., Schneeweiss et al., 2002). The intake of anticholinergic drugs considered as PIM can also increase the risk for subsequent dementia (e.g., Carrière et al., 2009; Jessen et al., 2010; Gray et al., 2015). Risacher et al. (2016) found that anticholinergic drug intake was associated with poorer cognitive performance, reduced brain metabolism, higher levels of brain atrophy, and an increased risk for clinical conversion to mild cognitive impairment or dementia in cognitively normal participants. Several different drug groups were summarized in the Priscus list by Holt et al. (2010) as potentially inappropriate for elderly patients in the German health care system. Besides other drugs like analgesics or antibiotics, several antidepressants are included in this list, because their intake is associated with an increased risk for delirious states or cognitive deficits due to anticholinergic effects (e.g., amitriptyline, doxepine, and imipramine (all tricyclic antidepressants (TCA)); cf. Holt et al., 2010). Nonetheless, these drugs are frequently prescribed even in patients with cognitive impairment. A German study found that antidepressant treatment in older patients aged 65 years and older was often initiated with TCA (Jobski et al., 2017). Wucherer et al. (2017) found that more than every fifth in a sample of community-dwelling primary care patients with dementia received at least one PIM, most frequently anticholinergic antidepressants and long-acting benzodiazepines.

Some findings on the association between the intake of antidepressant drugs and the subsequent risk for dementia exist, but results are rather inconsistent. In a population-based study of participants aged 65 and older, antidepressant drug use accompanied by persistent depressive symptoms was associated with a highly increased risk for dementia, but only in men (Fuhrer et al., 2003). In a nationally representative study of participants with an average age of 72 years, the use of antidepressant drugs did not modify cognitive decline over six years after the adjustment for depressive symptoms, medical comorbidity, and anticholinergic burden (Saczynski et al., 2015). However, Gray et al. (2015) found a dose-response relationship between anticholinergic properties exhibited by drugs like TCA and the risk of subsequent dementia over ten years. Interestingly, both selective serotonin reuptake inhibitor (SSRI) and non-SSRI antidepressants were associated with an increased risk for subsequent dementia over up to 18 years of follow-up in another study (Wang et al., 2016). Antidepressant drug intake was also associated cross-sectionally with an increased brain atrophy in an elderly sample without dementia (Geerlings et al., 2012). In a retrospective case-control study, Lee et al. (2016) found that most antidepressant drugs (e.g., SSRI, monoamine oxidase inhibitors (MAOI), heterocyclic antidepressants) were associated with a 1.5–2.5 fold increased risk for dementia, whereas TCA, surprisingly, were associated with a decreased risk for subsequent dementia. Kessing et al. (2009) showed in a register-based study that the intake of antidepressants (especially SSRI but also other classes) was associated with an increased risk for dementia, but the risk decreased with an increasing number of prescriptions, albeit it remained to be higher compared to non-users. On the other hand, some authors hypothesized that antidepressants might contribute to the dementia risk reduction (e.g., Bali et al., 2016) by increasing brain-derived neurotrophic factor (BDNF) levels (e.g., Caraci et al., 2010) or hippocampal neurogenesis (e.g., Dranovsky and Hen, 2006).

Hence, the results of the existing studies on the association between the intake of antidepressant drugs and subsequent risk for dementia are inconclusive. Few studies found no association or a reduced risk for subsequent dementia in case of antidepressant use. An association between depression and an increased risk for subsequent dementia was found in several studies (e.g., Ownby et al., 2006; Diniz et al., 2013) and depression itself was considered as a risk factor for or a prodrome of dementia. One might argue that a successful treatment of depression for example by the means of antidepressants might reduce the risk for subsequent dementia, if depression would be considered as a true risk factor for dementia. Several studies found an association between anticholinergic antidepressants (mainly TCA) and an increased risk for subsequent dementia, but there are also findings suggesting that SSRI might be associated with an increased subsequent dementia risk. The age of participants, the limitations of study designs, the length of follow-ups, and the classification of antidepressants might account for different results. Studies that included old and very old participants are rather scarce. Additionally, studies on the association between antidepressant drug intake and risk for subsequent dementia sometimes did not control for the severity of depressive symptoms and, even more frequently, did not control for the cognitive status. However, assessments of both depressive symptoms and cognitive status are necessary from our point of view. If an association between the intake of antidepressant drugs and the risk for subsequent dementia would disappear after the statistical control for depressive symptoms, this might indicate that patients with more depressive symptoms receive antidepressants more frequently and depression severity, but not antidepressants might explain a possible association. Additionally, several studies found (also in the present study cohort) that depression can have a prodromal association with subsequent dementia (e.g., Li et al., 2011; in AgeCoDe cohort: Heser et al., 2013). Thus, an association between the intake of antidepressant drugs and subsequent dementia might also be explained by mild cognitive deficits due to an early dementia process but not due to antidepressants. Therefore, the aim of our study was to investigate the association between the use of antidepressant drugs and subsequent dementia also after adjusting for depressive symptoms and global cognition besides other relevant covariates in an elderly study cohort using a longitudinal study design with long-term follow-up periods. We hypothesized that the intake of antidepressant drugs, primarily those considered as PIM by the Priscus list (Holt et al., 2010), would increase the risk for subsequent dementia. The results of our study might partly contribute to the validation of the Priscus list suggested by others (e.g., Amann et al., 2012).

2. Methods

2.1. Sample

We analyzed data from a German prospective multi-center study (the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe) and the Study on needs, health service use, costs and health-related quality of life in a large sample of oldest-old primary care patients (85+) (AgeQualiDe), which is a continuation (follow-up 7–9) and extension of AgeCoDe). Participants at least 75 years of age were recruited at baseline in 2003/2004 via general practitioners (GPs) in six German cities (Bonn, Düsseldorf, Hamburg, Leipzig, Mannheim, and Munich). Written informed consent was provided prior to participation. The study has been approved by the local ethics committees of all participating study centers and complied with the ethical standards of the Declaration of Helsinki as revised 1989. The interviews were conducted in person by trained research assistants. The sample initially consisted of 3327 participants. Follow-up assessments after baseline were conducted every 18 months until follow-up 6 and every 10 months afterwards until follow-up 8. Data of covariates and predictors assessed at baseline were used to predict the dementia status until follow-up 8 in survival analyses. Follow-up 8 was conducted approximately 12 years after baseline. Subjects who received a dementia diagnosis at baseline (n = 70) and subjects without information about their dementia status at any assessment (n = 18) were excluded. Sample characteristics are given in Table 1.

2.2. Covariates

In the adjusted analyses, we controlled for age at baseline (in years), sex (male and female), and education according to Casmin (König et al., 1988) as demographical covariates. Depressive symptoms at baseline were entered in a second step as a measure of depression severity. They