Antipsychotic Use and the Risk of Initiating Medication for Benign Prostate Hyperplasia in Persons With Alzheimer Disease

A Matched Cohort Study

Kim Orsel, BSc,† Heidi Taipale, PhD,†‡§ Sami Raatikainen, PhD, MD,|| Pasi Lampela, PhD, MD,†‡ Anna-Maija Tolppanen, PhD,† Marjaana Koponen, PhD,†‡ Antti Tanskanen, PhilLic,§¶ Jari Tiihonen, PhD, MD,§¶ Helga Gardarsdottir, PhD,* and Sirpa Hartikainen, PhD, MD†‡*

Abstract:

Background: Antipsychotics (APs) are known to exacerbate symptoms of benign prostate hyperplasia (BPH) and may even cause urinary retention. The anticholinergic effects of APs and their dopamine D_2- and α-receptor blockade may lead to voiding dysfunction of BPH patients. The objective of our study was to investigate whether the use of APs is associated with an increased risk of initiating medication for BPH in men with Alzheimer disease (AD).

Methods: Data from the nationwide MEDALZ (MEDication use and ALZheimer's disease) cohort, including all community-dwelling persons diagnosed with AD in Finland, were utilized. Register-based data included medication dispensing, comorbidities, and hospital discharge diagnoses. Men who initiated APs (n = 4579) were 1:1 matched with men who did not initiate APs (n = 4579), according to time since AD diagnoses and age. The risk of starting BPH medication was investigated with Cox regression.

Results: Among AP users, BPH medication was initiated to 345 persons (7.5%). Antipsychotic use was not associated with risk of initiating BPH medication (comorbidity-adjusted hazard ratio, 0.92; 95% confidence interval, 0.74–1.15) compared with no use of APs. In addition, no risk was found when AP drug substances were analyzed separately.

Conclusions: Use of APs did not increase the risk of initiating medication for BPH in men with AD.

Key Words: Alzheimer disease, antipsychotic, benign prostate hyperplasia, dementia, pharmacoepidemiology

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Alzheimer disease (AD) is a neurodegenerative disease and the most common cause of dementia. During the course of dementia, up to 97% of persons with AD develop behavioral and psychological symptoms of dementia (BPSD).[1] Antipsychotic (AP) drugs have frequently been prescribed for BPSD in AD, but their use has been associated with several serious adverse effects and events, such as an increased risk of hip fractures, strokes, and mortality.[2–5] Some APs are known to exacerbate symptoms of benign prostate hyperplasia (BPH) due to anticholinergic effects, and therefore some APs are contraindicated and should be avoided in persons with a prostate hyperplasia.[6]

From the *School of Pharmacy, Utrecht University, Utrecht, the Netherlands; †School of Pharmacy and ‡Kuopio Research Centre of Geriatric Care, University of Eastern Finland, Kuopio, Finland; §Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden; and ||Department of Urology, Kuopio University Hospital; and ¶Department of Forensic Psychiatry, Niuvanniemi Hospital, University of Eastern Finland, Kuopio, Finland.

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Reprints: Heidi Taipale, PhD, Kuopio Research Centre of Geriatric Care, University of Eastern Finland, PO Box 1627, 70211 Kuopio, Finland (e-mail: heidi.taipale@uef.fi).

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Benign prostate hyperplasia is common among older men, affecting approximately 50% of men older than 60 years, and by the age of 85 years, more than 90% have symptoms.[7] Most difficult symptom of BPH is urinary retention (UR), which requires immediate medical attention. Antipsychotics may cause residual urine or exacerbate urinary retention by various receptor interactions in the bladder. The anticholinergic activity, which interferes with cholinergic innervation of detrusor muscle, decreases the force of bladder detrusor contractions, which may lead to residual urine or even urinary retention.[8] Another mechanism is via the central serotoninergic effects, central dopamine D_2 blockade, and peripheral stimulation of the α_1-receptors of the urinary tract.[8] Serotonin facilitates urine storage by enhancing the sympathetic reflex pathway and inhibiting the parasympathetic voiding pathway. Blocking central D_2-receptors inhibits the facilitation of the voiding, and the peripheral stimulation of the α_1-adrenoreceptors leads to contraction of the internal sphincter and relaxation of the detrusor muscle. These effects could lead to residual urine and urinary retention among users of APs.[8–10]

To our knowledge, no previous studies have focused on assessing the initiation of medication for BPH after AP use in persons with AD. The aim of this research was to determine the risk of initiating BPH medication after AP use.

MATERIALS AND METHODS

Data from the nationwide MEDication use and ALZheimer's disease (MEDALZ) study was utilized. The MEDALZ study has been described in detail elsewhere.[11] In brief, this cohort included all community-dwelling persons who received their first clinically verified AD diagnosis between 2005 and 2011 in Finland (n = 70,718). Data in the MEDALZ study has been linked to several nationwide registers including the Prescription Register, Special Reimbursement Register, and Hospital Discharge Register. No ethics committee approval was required, as data were deidentified, and participants were not contacted.

For this study, only men 50 years or older from the MEDALZ cohort were included (n = 24,561). A new user design was used to avoid the mistake of adjusting for factors on the causal pathway, which may introduce bias toward the null.[12] Those who initiated an AP after AD diagnosis were considered as users and matched with 1 control person who did not use APs at the matching date (ie, initiation of AP use for the case); 1:1 matching according to time since AD diagnoses (±0.5 years) and age (±2 years) was conducted by incidence density sampling. For both AP users and AP nonusers, a 1-year washout period for AP use and BPH medication use was introduced before the AP initiation or the corresponding matching date for nonusers. Persons using either APs or BPH medication during this period were excluded. In addition, persons with schizophrenia/bipolar disorder (*International Classification of Diseases, 10th Revision* codes F20-31) were excluded to restrict AP

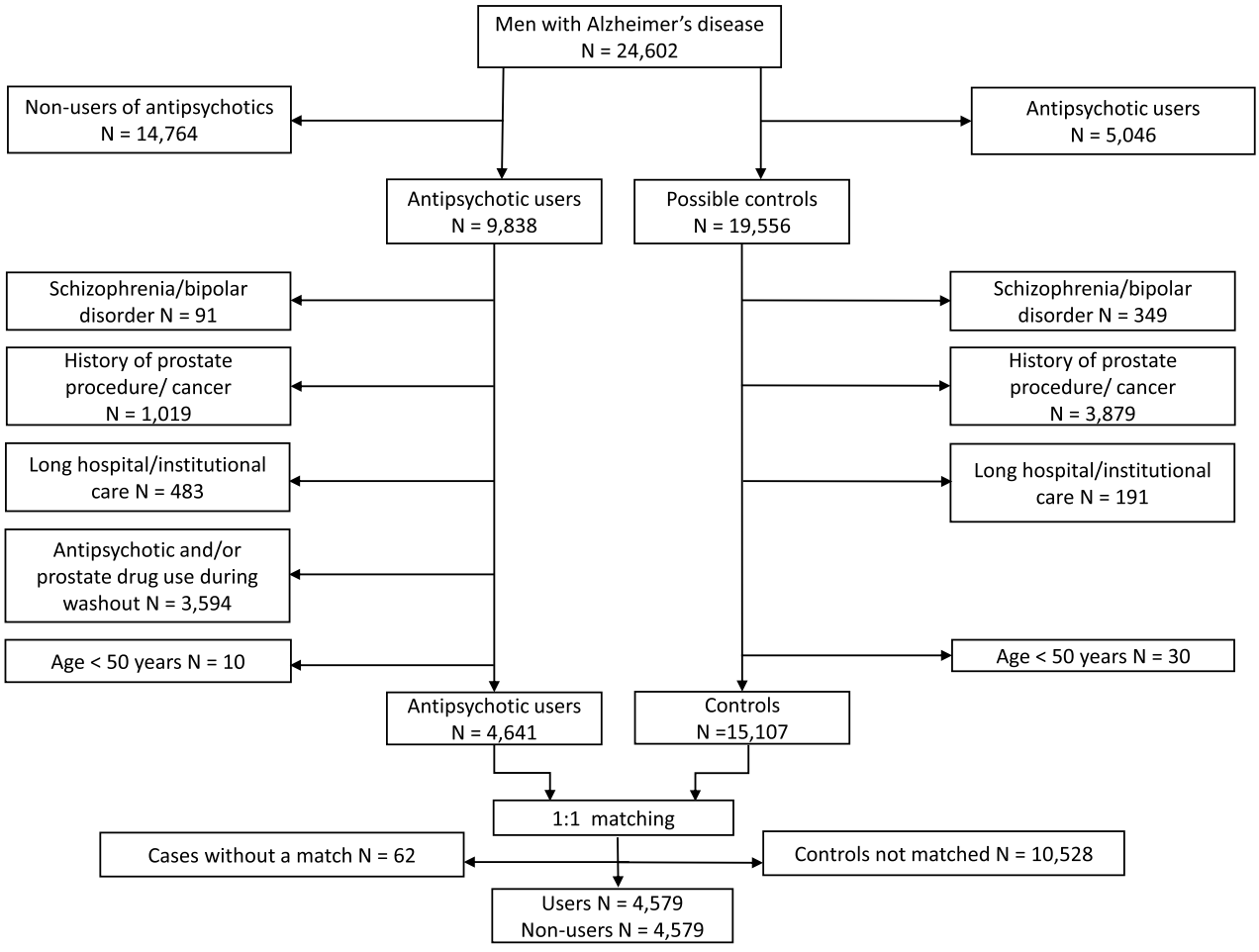

FIGURE 1. Flow chart of exclusions conducted for this study.

use for BPSD symptoms (Fig. 1). Also, those with previous prostate procedure (NCSP codes KED22, KED33, KED52, KEC00, KEC01) or history of prostate cancer (*International Classification of Diseases, 10th Revision* code C61) were excluded. Controls could become AP users during the follow-up (and consequently, censored from being controls) and were matched in the same way.

Use of APs (ATC code N05A, excluding N05AN01–lithium) was defined as the exposure, and the primary outcome was initiation of BPH medication (ATC code G04C) during follow-up. Drugs included in this ATC group include α-adrenoreceptor antagonists (such as alfuzosin, tamsulosin) and testosterone-5-α reductase inhibitors (finasteride, dutasteride). The follow-up started at the initiation of AP use (and at the corresponding matching date for nonusers) and ended when one of the following was first to happen: discontinuation of AP use, outcome (start of BPH medication), death, long hospitalization/institutionalization (≥90 days), start of AP use for nonusers, or the end of study follow-up (December 31, 2015).

Initiation of BPH medication was considered as a marker for residual urine and/or UR, although BPH medication may also be used in other conditions such as chronic prostatitis, urolithiasis expulsion therapy, or prostatic cancer, but these being rare indications. With the PRE2DUP method, which models drug utilization from prescription register data, drug use periods and time-dependent exposure to APs and BPH medication were constructed.[13] During a drug use period of "any AP," persons could switch between different drug substances of APs (n = 4579). When investigating the risk of the outcome for different AP substances, only the first AP substance of a person was assessed, and analyses were restricted to those initiating with AP monotherapy (n = 4539). In this analysis, follow-up was censored if the person switched APs.

Analyses were adjusted for potential confounding factors. These included use of drugs for urinary frequency and incontinence (G04BD; including oxybutynin, tolterodine, solifenacin, trospium, darifenacin, fesoterodine, and mirabegron), tricyclic antidepressants (N06AA), loop diuretics (C03CA), and acetylcholine esterase inhibitors (N06DA) and were defined at the start of follow-up. Comorbidities included epilepsy, asthma/chronic obstructive pulmonary disease, diabetes, and cardiovascular disease (chronic heart failure, hypertension, coronary artery disease, and/or chronic arrhythmia), defined from the Special Reimbursement Register.

Descriptive statistical analyses were undertaken using means, SDs, and percentages. Risk of BPH medication initiation was analyzed with Cox regression models and reported as hazard ratio (HR) and adjusted HR (HR_{adj}) with 95% confidence intervals (CIs). Adjusted HRs were adjusted for comorbidities and other drug use (Table 1). The covariates were chosen on the basis of previous literature as risk factors for BPH and potentially

TABLE 1. Characteristics of Matched AP Users and Nonusers With AD

	Users (n = 4579), n (%)	Nonusers (n = 4579), n (%)	*P*
Age (SD), y	79.2 (7.4)	79.3 (7.3)	*Matched*
Time since AD diagnosis, d	876	877	*Matched*
Asthma/COPD, n (%)	342 (7.5)	385 (8.4)	0.66
Cardiovascular disease, n (%)	2227 (48.6)	2329 (50.9)	0.07
Diabetes, n (%)	683 (14.9)	772 (16.9)	0.66
Epilepsy, n (%)	109 (2.4)	144 (3.1)	0.29
Drugs for urinary frequency and incontinence, n (%)	65 (1.4)	118 (2.6)	0.08
Loop diuretics, n (%)	812 (17.7)	767 (16.8)	0.74
Tricyclic antidepressants, n (%)	15 (0.3)	22 (0.5)	0.85
Acetylcholine esterase inhibitors, n (%)	2977 (65.0)	3066 (67.0)	0.68

COPD indicates chronic obstructive pulmonary disease.

associated with AP use. All analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC).

RESULTS

The study population consisted of 4579 AP users and 4579 matched nonusers. The mean age of AP users was 79.2 (SD, 7.4) years, and for nonusers, it was 79.3 (SD, 7.3) years. Other characteristics of the study population are shown in Table 1. The mean follow-up time for nonusers was 756 (SD, 644) days, and for AP users, it was 398 (SD, 477) days. There were no significant differences in prevalence of comorbidities and other drug use between users and nonusers.

The number of men who started BPH medication after AD diagnosis in the AP users group was 345 (7.4 persons per 100 person-years of AP use), and in the matched control group, it was 664 (7.0 persons per 100 person-years of nonuse) (Table 2). Antipsychotic use was not associated with risk of BPH medication initiation (unadjusted HR, 1.04 [95% CI, 0.87–1.24]; HR_{adj}, 0.92 [95% CI, 0.74–1.15]). When the follow-up time was restricted to 1 year, the HRs did not change significantly (unadjusted HR, 0.90 [95% CI, 0.76–1.06]). When most frequently used AP substances were analyzed separately and compared with nonusers, there were no significant differences in the risk of the outcome (Table 2).

DISCUSSION

We found that among men with AD users of any APs had no higher risk of initiating BPH medication than nonusers. Also, when AP drug substances were assessed individually, no significant differences in initiation of BPH medication were found between users and nonusers.

To our knowledge, no previous studies have been conducted on the risk of initiating BPH medication after use of APs in men with AD. The use of APs has been associated with exacerbating symptoms of BPH.[6] The anticholinergic effects of APs and their D_2- and α_1-adrenergic receptor blockade may increase the risk of symptoms of BPH and urinary retention.[9,10] The stimulation of α_1-receptor leads to contraction of the internal sphincter, so α-inhibition should lead to relaxation of sphincter muscle, making voiding easier (eg, the effect of tamsulosin is based on this). However, this α-receptor matter is not that straightforward, as the atypical AP clozapine may also cause urinary incontinence in addition to urinary retention, likely because of its α-inhibitory properties.[9] By using APs, the risk of initiating BPH medication to suppress the symptoms of BPH or treat urinary retention may be increased.

TABLE 2. Risk of BPH Medication Initiation Associated With AP Use in General and With Specific APs Among Men With AD

	No. Persons	Person-Years	Initiation of BPH Medication, n	Incidence Rate per 100 Person-Years (95% CI)	$HR_{unadjusted}$ (95% CI)	HR_{adj} (95% CI)
Nonusers	4579	9479	664	7.00 (6.95–7.06)	*Reference*	*Reference*
AP users	4579	4655	345	7.41 (7.33–7.49)	1.04 (0.87–1.24)	0.92 (0.74–1.15)
Risperidone	2768	2333	182	7.80 (7.69–7.91)	1.05 (0.80–1.37)	1.01 (0.76–1.34)
Quetiapine	1388	1559	108	6.93 (6.80–7.06)	0.80 (0.55–1.15)	0.80 (0.54–1.19)
Haloperidol	196	89	8	8.99 (8.37–9.61)	1.50 (0.42–5.32)	1.13 (0.36–3.60)
Olanzapine	69	61	3	4.92 (4.36–5.47)	0.33 (0.04–3.20)	0.37 (0.04–3.58)
Levomepromazine	20	18	3	16.67 (14.78–18.55)	1.00 (0.06–15.99)	1.13 (0.07–18.75)
Other APs	98	74	5	6.76 (6.16–7.35)	0.67 (0.11–3.99)	0.54 (0.10–3.01)

Hazard ratios are adjusted for comorbidities (asthma/chronic obstructive pulmonary disease, cardiovascular diseases, diabetes, epilepsy) and use of drugs for urinary frequency and incontinence, loop diuretics, tricyclic antidepressants, and acetylcholine esterase inhibitors. Other APs included chlorpromazine, periciazine, melperone, flupentixol, chlorprothixene, zuclopenthixol, clozapine, sulpiride, and aripiprazole.

One possible explanation for the lack of association is that APs are often used in very low doses among persons with AD.[14] However, we could not analyze the used AP doses because obtained doses are average doses during the whole drug use period and are not restricted to time before or after initiation of BPH medication. Therefore, the average doses may not represent the dose that was used before initiating BPH medication.

Benign prostate hyperplasia medication initiation was considered as a proxy for UR, as UR is unlikely to lead to hospitalization, and we did not have data on primary care visits because of UR. Urinary retention related to AP use should be managed by discontinuing the use or by reducing the dose.[9] However, discontinuation or dose reduction is not always possible because of a lack of treatment options and already low doses,[14] and in these situations, initiation of BPH medication is the only treatment option. Thus, as UR is likely to be treated with BPH medication, we considered this as a suitable proxy measure.

In conclusion, the use of APs in men with AD is not associated with a higher risk of initiating medication for BPH.

AUTHOR DISCLOSURE INFORMATION

J.T. has served as a consultant to Lundbeck, Organon, Janssen-Cilag, Eli Lilly, AstraZeneca, F. Hoffman-La Roche, and Bristol-Myers Squibb. He has received fees for giving expert opinions to Bristol-Myers Squibb and GlaxoSmithKline; lecture fees from Janssen-Cilag, Bristol-Myers Squibb, Eli Lilly, Pfizer, Lundbeck, GlaxoSmithKline, AstraZeneca, and Novartis; and a grant from the Stanley Foundation. J.T. is a member of advisory boards at AstraZeneca, Janssen-Cilag, and Otsuka. S.H. has received a lecturing fee from MSD. H.T., J.T., and A.T. have participated in research projects funded by Janssen and Eli Lilly with grants paid to the institution where they were employed. A.T. is a member of the Janssen advisory board. M.K. has received a personal research grant from Oy H. Lundbeck Ab foundation outside the submitted work. The other authors declare no conflicts of interest.

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