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Antipsychotic drug use associated with urinary tract infections in older women

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ABSTRACT

Objectives: Antipsychotic drugs are frequently prescribed to elderly patients, but they are associated with serious adverse effects. The objective of the current study was to investigate the association between use of antipsychotics by elderly women and the risk of urinary tract infections (UTIs).
Cohort study setting: Dispensing data were obtained from the PHARMO Database Network for the period 1998–2008.
Participants: Ambulatory Dutch women (≥65 years) with current and past use of antipsychotics.
Measurements: Incidence rates of UTIs, as defined by use of nitrofurantoin, was calculated within and outside the period of exposure to antipsychotic drugs. Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was used to calculate crude and adjusted hazard ratios (HRs).
Results: During the study period, 18,541 women with a first prescription of an antipsychotic were identified. Current use of antipsychotics was associated with an increased risk of UTI compared to past use: HR, adjusted for age and history of UTIs, 1.33, 95% CI 1.27–1.39. A strong temporal relationship was found: the risk of being treated for a UTI was higher in the first week after the start of the treatment (adjusted HR 3.03, 95% CI 2.63–3.50) and decreased after 3 months (adjusted HR 1.22, 95% CI 1.17–1.28). Cumulative exposure was not associated with an increased risk of UTIs. There was no difference in effect between conventional and atypical antipsychotics.
Conclusion: Our results show an increased risk of uncomplicated UTIs during antipsychotic use in older female patients, especially in the first week of treatment.

1. Introduction

Antipsychotic drugs are approved for the treatment of schizophrenia and bipolar disorder [1]. While they are frequently prescribed to older patients, atypical antipsychotics are often used outside their approved indication, to treat behavioral disturbances in elderly patients with dementia [1]. A recent study in the United Kingdom reports a rather high prevalence of antipsychotic drug use of 1% in a primary care setting [2]. Yet, these drugs may cause serious adverse effects. In 2008, the Food and Drug Administration reported that the use of antipsychotics to treat behavioral disorders in elderly patients with dementia was associated with an increased mortality rate [3,4]. Although the cause of this increased mortality is not completely understood, antipsychotic drug use is associated with an increased risk of cardiovascular events, such as stroke, thrombo-embolic events, and cardiac arrhythmia, and infections, such as pneumonia [5]. The risk of bacterial infections was found to be higher in nursing home residents starting conventional antipsychotics than in similar residents starting atypical antipsychotics [6].

Although these drugs increase the risk of bacterial infection, such as pneumonia, it is unclear whether this is also the case for urinary tract infections (UTIs). Urinary tract problems, such as

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incontinence and urine retention, are reported in users of both typical and atypical antipsychotics [7]. These problems may be caused by extrapyramidal side effects, due to anticholinergic side effects or peripheral α1-adrenergic blockade, and may increase the susceptibility to UTIs [7]. UTIs are very common in the elderly population [8]. In The Netherlands, in primary care there are on average 70 episodes of UTIs per 1000 patients–year in women of all ages, with the highest incidence in women >60 years old [9].

Since UTIs are a major cause of morbidity and mortality in elderly people and antipsychotic drugs are prescribed frequently to these individuals, an association between these two factors would be clinically relevant. Therefore, the aim of this study was to investigate the association between antipsychotic use in elderly women and the risk of UTIs.

2. Methods

2.1. Design

This population-based cohort study involved ambulatory Dutch female patients ≥65 years with current and past use of antipsychotics, with or without the occurrence of an uncomplicated UTI.

2.2. Setting

Data were obtained from the PHARMO Database Network (Pharmo Institute, Utrecht, The Netherlands; available at: http://www.pharmo.nl). The PHARMO database network includes the pharmacy dispense records of over 3 million community-dwelling residents in The Netherlands from 1998 onward. Patient information includes gender and date of birth. Because most patients in The Netherlands are registered with a single community pharmacy, records are virtually complete with regard to prescription drugs [10]. The computerized drug-dispense histories contain information about the dispensed drug, dispense date, the prescriber, amount dispensed, and the prescribed dosage regimen. The dispense date is the day the patient or caregiver picked up the prescription at the pharmacy. The duration of use of each dispensed drug can be estimated from the database by dividing the number of dispensed units by the prescribed number of units to be used per day. The database does not provide information about the indications for use of the medication or registration of non-prescription medication. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. All PHARMO-linked research is in accordance with Dutch privacy and ethical regulations.

2.3. Participants

Female patients (≥65 years) with at least one prescription of an antipsychotic drug between 1998 and 2008 were identified. Drugs starting with the four-digit ATC code N05A (with the exception of lithium) were classified as antipsychotics. The date of the first antipsychotic prescription marked the start of follow-up. Patients were then followed up until the end of the study period, the censoring date in the database, or death of the patient, whichever came first. All patients were eligible for inclusion if they had one year of prior history in PHARMO before the start of follow-up. The rationale for including female patients only was because we defined our study outcome of uncomplicated UTI on the basis of the use of nitrofurantoin, which is the first-choice drug for treating uncomplicated UTIs in women in The Netherlands, but not in men [9].

2.4. Exposure definition

Exposure was defined as the use of antipsychotic drugs. For all patients, we classified follow-up time into periods of current use and past use of antipsychotics. To assess periods of current use, treatment episodes were constructed. Antipsychotic treatment episodes were established by summing consecutive drug deliveries by the pharmacy [11]. If an antipsychotic prescription with the same drug was collected by the patient before the theoretical end date of the previous prescription, the number of overlapping days (units at home) was added to the end date of the subsequent antipsychotic prescription. We allowed for a 14-day permissible gap between the theoretical end date of an antipsychotic prescription and the next one. We created separate treatment episodes for individual antipsychotic initially, and combined these episodes to allow concurrent use of multiple types of antipsychotic drugs. If the duration of a subsequent prescription overlapped that of a subscription for another antipsychotic, the patient was considered to have switched therapy and the remaining tablet days from the first prescription were disregarded. After the end of a treatment episode, patients were classified as past users, until a new treatment episode occurred. We chose past antipsychotic use as reference period, because the patient characteristics were then comparable in both timeframes. To allow for time-dependent updates of covariates e.g. potential confounders, periods of current and past use were split into periods of maximally 182 days. The first 14 days of past use were considered a washout period where no events were counted.

Periods of current use were further stratified according to:

(I) duration (of each current use episode, not cumulatively over follow-up) in 1–7, 8–14, 15–30, 31–90, >90 days;
(II) mean number of standardized defined daily doses (DDD) per day, this is the assumed average maintenance dose per day of a drug used for its main indication in adults and is defined by the World Health Organization (WHO) [12]. For example, the DDD of haloperidol is 8 mg per day for the treatment of psychosis in adults. In general, older patients receive lower doses of antipsychotic medications than younger patients. We used DDD to create comparative doses for different drugs with different potencies. The DDD was categorized into <0.125, 0.125–0.5, and >0.5 DDD.
(III) type of antipsychotic: 1) use of atypical antipsychotics (clozapine, olanzapine, quetiapine, tetrabenazine, sulpiride, tiapride, risperidone, aripiprazole); 2) use of conventional antipsychotics (bromperidol, chlorprothixene, droperidol, fluphenazine, flupentixol, fluspirilene, haloperidol, lurasidone, paliperidone, penfluridol, perphenazine, periciazine, pimozide, pipamperone, sertindole, zuclopenthixol); 3) concurrent use of more than one antipsychotic agent.

2.5. Outcome definition: recurrent events

The outcome of interest was the occurrence of uncomplicated UTI. Since the Pharmo database used does not contain medical diagnoses in general practice, the prescription of a therapeutic dosage of nitrofurantoin (50 mg 4 times a day or 100 mg 2 times a day) was used as proxy for uncomplicated UTI. In general, uncomplicated UTI is the sole indication for nitrofurantoin, except for UTI prophylaxis. If a patient received a second prescription of nitrofurantoin within 7 days after the first prescription ended, this was considered one event (cluster). During the event (cluster of days) the patient was not at risk of a recurrent event. As patients may experience several episodes of UTIs, we assessed the occurrence of recurrent UTIs during the whole follow-up period.

2.6. Potential confounders

Known risk factors for UTIs that could potentially confound the relationship between antipsychotic drug use and UTIs are age [13], history of UTIs [13], diabetes mellitus [9], being immune