Association Between Urinary Tract Infections and Antipsychotic Drug Use in Older Adults

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Abstract:

Background: Antipsychotic drugs are frequently prescribed to older adults, but they may be associated with serious adverse effects. The objective was to investigate the association between use of antipsychotics in older adults and the risk of urinary tract infections (UTIs).

Methods:

Design: This study was designed as a cohort study.

Setting: Data were obtained from the Clinical Practice Research Datalink from January 1, 2000, to September 29, 2016.

Participants: Primary care patients 65 years or older in the United Kingdom with a first prescription for an oral antipsychotic were included in the study.

Measurements: Incidence of UTIs was calculated for periods with and without exposure to antipsychotic drugs in one cohort. Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was used to calculate hazard ratios (HRs) with 95% confidence interval (CI).

Results: During the study period, 191,827 individuals with a first prescription for an oral antipsychotic drug were identified. Current use of antipsychotics was associated with an increased risk of UTI compared with past use (adjusted HR, 1.31; 95% CI, 1.28–1.34). This effect was strongest in the first 14 days of use (adjusted HR, 1.83; 95% CI, 1.73–1.95) and in individuals who used more than one antipsychotic drug concomitantly (adjusted HR, 1.64; 95% CI, 1.45–1.87). The risk was slightly higher for typical antipsychotics than for atypical antipsychotics. Stratification by sex showed that risk estimates were slightly higher in men than in women.

Conclusions: Use of antipsychotics was associated with an increased risk of UTIs in both men and women, particularly in the first weeks after the start of treatment.

Key Words: antipsychotics, urinary tract infection, elderly

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Antipsychotic drugs are frequently prescribed to older adults. A recent study in the United Kingdom reported a prevalence of antipsychotic drug use of 1% in a primary care setting.[1] However, antipsychotics may cause serious adverse effects, and treatment indications are not always rational.[1] For instance, antipsychotics are still commonly prescribed to people with a diagnosis of dementia, contrary to clinical guidelines.[1] In 2008, The Food and Drug Administration determined that the treatment of behavioral disorders with antipsychotics in older adults with dementia was associated with increased mortality,[2,3] although the causes of this increased mortality are not completely understood. Potential explanations include that antipsychotic drug use is associated with an increased risk of cardiovascular events (eg, stroke, thromboembolic events, cardiac arrhythmia) and infections (eg, pneumonia).[4] A recent study in which the prescription of nitrofurantoin was used as proxy for uncomplicated urinary tract infections (UTIs) showed an increased risk of uncomplicated UTIs in women using antipsychotic drugs.[5] A strong temporal relationship was found, with the risk of being treated for an UTI being higher in the first week of treatment (adjusted hazard ratio [HR], 3.03; 95% confidence interval [CI], 2.63–3.50) and decreasing after 3 months (adjusted HR, 1.22; 95% CI, 1.17–1.28).[5] Urinary tract infections are a common problem in older adults, in residents of long-term care facilities, and in hospitalized patients. Indeed, in these first 2 populations UTIs are the number 1 cause of infection.[6] It is unknown whether the observed risk of uncomplicated UTIs can be extrapolated to all UTIs and to male users of antipsychotics.

The objective of the current study was to investigate the association between use of antipsychotics in older men and women and the risk of UTIs, both complicated and uncomplicated.

METHODS

Design

This study was designed as a cohort study of adults (≥65 years) in primary care with current or past use of antipsychotics. Periods with and without antipsychotic use were compared within one cohort on the incidence of urinary tract. Otherwise, the older adults are their own control group, and only different time frames are compared.

Setting

Data were obtained from the Clinical Practice Research Datalink (CPRD; http://www.CPRD.com), an anonymized database containing computerized medical records of 674 primary care practices in the United Kingdom, representing 6.9% of the population.[7,8] Data recorded in the CPRD include demographic information, prescription details, clinical events, specialist referrals, hospital admissions, and major outcomes since 1987.[7] Primary care diagnoses are recorded in the CPRD, using a hierarchical clinical coding system (Read codes).[7]

The study protocol was approved by the Independent Scientific Advisory Committee of CPRD (protocol number 16_272R). Patient information is only available anonymized and de-identified in the database, and hence, informed consent was not needed from patients.

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Participants

Older adults 65 years or older with at least one prescription for an antipsychotic in the period January 1, 2000 to September 29, 2016, were identified in the CPRD. Only people with at least 1 year of valid history, before their first prescription of antipsychotic drug, were included. This was to verify the previous drug use and history of UTIs. The date of the first antipsychotic prescription marked the start of follow-up. Older adults were followed up until the end of the study period, transfer out of the practice, last collection date for the practice, the date of a first prescription of an injectable antipsychotic, or death of the patient, whichever event occurred first. Figure 1 shows the flowchart of the inclusion from CPRD.

Exposure Definition

Exposure was defined as the use of antipsychotic drugs. Follow-up for each patient was classified into periods of antipsychotic use (current use, that is, exposed) and periods of nonuse (past use, that is, nonexposed); older adults could switch between periods of current and past use. We chose past antipsychotic use as reference because the patient characteristics were then comparable in both time frames. Figure 2 shows this method graphically.

Antipsychotic drug use was defined as the use of oral antipsychotics, such as tablets and solutions, because the duration of treatment episodes is not always clear with depot (injectable) formulations. Prescriptions were retrieved from the CPRD. Information on general practitioner-prescribed medications was extracted using appropriate British National Formulary medicine codes. For all older adults, antipsychotic treatment episodes were constructed using the method of Gardarsdottir et al.[9] A treatment episode was defined as a series of successive prescriptions for antipsychotics written out by the general practitioner, taking dose changes, and product changes into account. If a new prescription for the same antipsychotic was issued 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. If a different strength of the same type of antipsychotic was prescribed, the remaining days were reset to

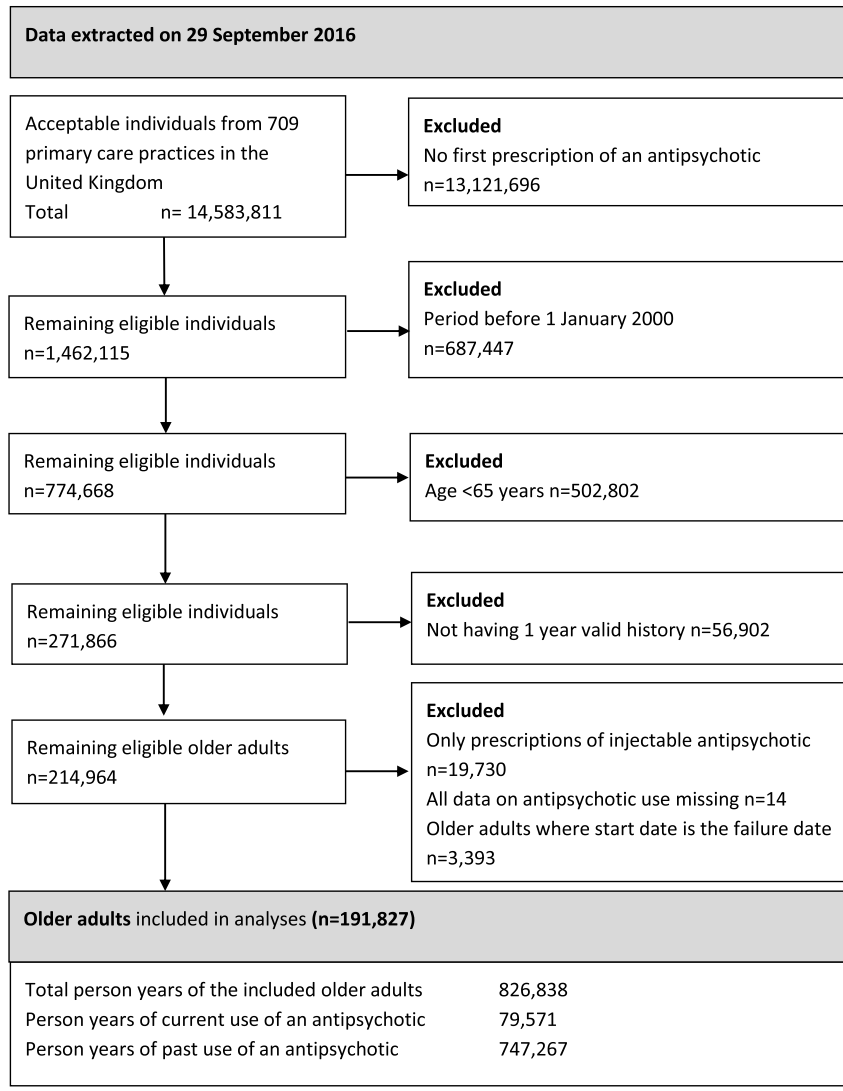

FIGURE 1. Flowchart of the inclusion from CPRD.

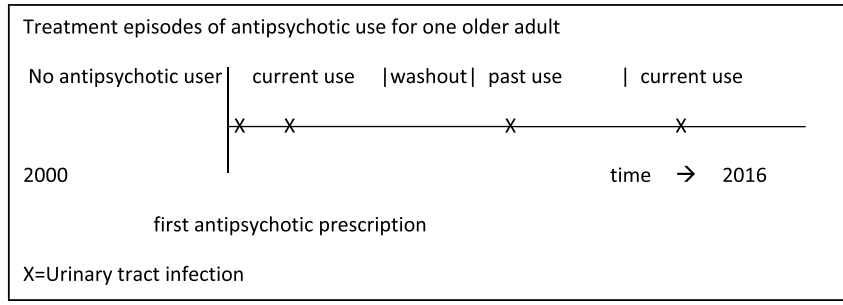

FIGURE 2. Methods.

zero. We used a 14-day permissible gap between the end date of one prescription and the start of the next prescription, to allow for irregular use. If the next prescription started more than 14 days after the end of the old prescription, we considered it a new treatment episode.[9] We created separate treatment episodes for individual antipsychotics initially, and combined these episodes to allow for concurrent use of multiple types of antipsychotic drugs. After each treatment episode, a washout period of 14 days was applied in which the patient was deemed not at risk of a study outcome. After the washout period, an episode of past use started (the reference period).

Periods of current antipsychotic use were then further stratified according to the following:

(I) *Duration* (of each treatment episode, not cumulatively over follow-up) in 1–14, 15–30, 31–90, and >90 days
(II) Standardized *defined daily doses* (DDDs): this is the assumed average maintenance dose per day for a drug used for its main indication in adults and is defined by the World Health Organization.[10] For example, the DDD of haloperidol is 8 mg/d for the treatment of psychosis in adults. In general, older adults receive lower doses of antipsychotics than younger adults. DDD was categorized into less than 0.125, 0.125–0.5, and more than 0.5 DDD.
(III) *Type of antipsychotic*:
(1) use of atypical antipsychotics (clozapine, olanzapine, quetiapine, amisulpiride, sulpiride, risperidone, aripiprazole),
(2) use of typical antipsychotics (benperidol, chlorpromazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, lurasidone, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sertindole, thioridazine, trifluoperazine, zotepine, zuclopenthixol); and
(3) concomitant use of more than one antipsychotic agent

Outcome Definition

Events were defined as diagnosis of an UTI, as assessed by clinical diagnoses and referrals. Because older adults can experience several UTIs a year, we assessed the occurrence of UTIs during the entire follow-up period. The duration of one event was the date of the diagnosis of UTI plus 7 days. If a patient had a second diagnosis of UTI within 30 days, this was considered as one event, or cluster. Urinary tract infections were defined as Read codes for UTIs, uncomplicated UTI, cystitis, prostatitis, urosepsis, or pyelonephritis. We did not use therapy as outcome because antibiotics for complicated UTIs are prescribed for several indications other than UTIs.

Potential Confounders

We selected the following known risk factors for UTIs as potential confounders for the relationship between antipsychotic drug use and UTI: age,[11] sex,[12] recurrent UTIs,[11] diabetes mellitus,[12] immunosuppressive medication,[12] stroke,[11] urine incontinence,[11] cognitive impairment or dementia,[11] disability in activities of daily living,[11] presence of a cystocele,[13] catheterization,[13] kidney stones or anomalies of the kidney or urinary tract,[12] urinary retention,[14] and malignancy.[14] Radiotherapy and surgery for prostate cancer or prostatic processes[14] are additional risk factors for UTIs in men. Unfortunately, we could not adjust for disability in activities of daily living reported in the CPRD. The other potential confounders were retrieved from medical records using Read codes and added as covariates.

Data Analysis

Hazard ratios were calculated for the association between current or past use of antipsychotics (reference period) and the risk of UTI within one cohort. The occurrence of an event (UTI) influences the risk of other events. This means that the analysis of recurrent events is complicated by the dependence on related events. Therefore, Cox proportional hazard regression analysis with Andersen-Gill extension for recurrent events was chosen to calculate crude and adjusted HRs for the association between current use of antipsychotics and risk of UTI in comparison to past use (reference period). To allow for time-dependent updates of covariates, exposed and nonexposed periods were split into periods of maximally 182 days, if necessary. Confounders were added sequentially to the model as follows: age, sex, comorbidity, and drugs. Beside age and sex, covariates were included in the final multivariate model if they induced a change in β coefficient of at least 10% for the individual covariates. We performed a separate analysis in which we censored older adults after their first UTI event. In this analysis, we did not look at recurrent events. Furthermore, we stratified the data for sex.

Data analysis was conducted using STATA SE 14. *P* values of less than 0.05 were considered statistically significant.

RESULTS

During the study period, 191,827 older adults with a first prescription of an oral antipsychotic drug were identified (63.7% women; mean age, 77 years). The characteristics of the study population are shown in Table 1. In total, 84,499 UTIs occurred in 38,887 unique older adults. The incidence of UTIs among current antipsychotic users was 152.7/100 person-years versus 96.8/100 person-years in the reference period, during past use, yielding an incidence rate ratio of 1.58.

On Cox regression analysis, current use of antipsychotics was found to be associated with a 30% increased risk of UTI compared with past use (adjusted HR, 1.31; 95% CI, 1.28–1.34; Table 2). Adjustment for age and dementia lowered the magnitude of the effect, but it remained statistically significant. Dementia

TABLE 1. Characteristics of Study Population

Characteristic	Overall (n = 191,827) No. (%)	Men (n = 69,624) No. (%)	Women (n = 122,203) No. (%)
Female	122,203 (63.7)		
Mean age (SD), y	77.9 (8.0)	76.1 (7.5)	77.5 (8.2)
History of UTI	52,466 (27.4)	12,097 (17.4)	40,369 (33.0)
Urine incontinence	2317 (1.2)	720 (1.0)	1597 (1.3)
Urinary retention	609 (0.3)	541 (0.8)	68 (0.1)
Catheterization	648 (0.3)	496 (0.7)	152 (0.1)
Cystocele or prolapse	12,442 (6.5)	998 (1.4)	11,444 (9.4)
Kidney stones or anomalies of kidney or urinary tract	89 (0.1)	50 (0.1)	39 (0.0)
Male: radiotherapy or surgery for prostate cancer	4652 (6.7)	4652 (6.7)	n/a
Stroke	13,163 (6.9)	5939 (8.5)	7224 (5.9)
Diabetes mellitus	25,236 (13.2)	11,261 (16.2)	13,975 (11.4)
Malignancy	43,758 (22.8)	18,906 (27.2)	24,852 (20.3)
Cognitive impairment or dementia	15,731 (8.2)	5862 (8.4)	9869 (8.1)
Immune compromised: using systemic glucocorticoids or immunosuppressants or having diagnosis of HIV	16,858 (8.8)	6395 (9.2)	10,463 (8.6)

was the only confounder that changed the β coefficient by more than 10%.

We found 75,377 events of uncomplicated UTIs (89.2%), 462 events of prostatitis (0.5%), 764 events of pyelonephritis or urosepsis (0.9%), and 7891 events of recurrent UTI (9.3%), and 5 events of UTI in pregnancy (0.0%, probably misclassified).

We found a slightly higher increased risk of UTI with current use of antipsychotics compared with past use when we censored older adults after the first UTI event (HR, 1.94; 95% CI, 1.89–2.00; adjusted for age and sex HR, 1.80; 95% CI, 1.76–1.85) and (full-adjusted HR, 1.55; 95% CI, 1.51–1.60).

The UTI risk was slightly higher for current use of typical antipsychotics (adjusted HR, 1.37; 95% CI, 1.33–1.41) than for current use of atypical antipsychotics (adjusted HR, 1.24; 95% CI, 1.21–1.28). The strongest effect was found in the first 14 days of current use (adjusted HR, 1.83; 95% CI, 1.73–1.95) and in older adults who were current users of more than one antipsychotic drug concomitantly (adjusted HR, 1.64; 95% CI, 1.45–1.87). Stratification by sex showed that risk estimates were slightly higher in men than in women. We did not perform analysis stratified for complicated UTIs because only 0.9% of the events were classified with a Read code for urosepsis or pyelonephritis. Table 2 also shows the results with the differences between men and women.

DISCUSSION

To our knowledge, this is the second study to report an increased risk of UTIs in older adults currently using antipsychotics. Our previous study showed an increased risk of being treated with nitrofurantoin for an uncomplicated UTI in older female users of antipsychotics in a Dutch population.[5] Urinary tract infections are more common in women than in men, with the highest incidence in women older than 60 years. Table 1 shows that 33% of the women have a history of UTI versus 17.4% in men. This study shows an increased risk of all UTIs in male and female users, with a slightly higher risk in men than in women. All UTIs in men should be considered complicated UTIs; the UTIs in women were most uncomplicated UTIs (99%). The antipsychotic-associated increased risk occurred primarily in the first 2 weeks of treatment. It is possible that older adults had a delirium caused by a UTI, so that the relation is the other way around, protopathic bias. However, this is less likely for older adults who were prescribed an antipsychotic first and who had a UTI of more than 14 days after the start of the antipsychotic.

In terms of the duration of the study period, the data span from 2000 through 2016. The prescribing patterns of antipsychotics have changed within this period because of the later introduction of atypical antipsychotics. The UTI risk was slightly higher for current use of typical antipsychotics than for current use of atypical antipsychotics, but was found in both groups.

The observed association between current antipsychotic use and UTI could be related to the antipsychotic itself or to the underlying disease or psychosis. Although the potential mechanisms underlying the association remain largely unknown, several mechanisms have been proposed. For instance, urinary tract problems, such as incontinence and urine retention, both of which increase susceptibility to UTIs, are reported in users of both typical and atypical antipsychotics.[15] First-generation antipsychotics that act predominantly on dopamine D2 receptors are not selective and cause a variety of side effects—D2-receptor antagonists influence the capacity and residual volume of the bladder, external urethral sphincter function, and the relaxation pressure and volume of urine at micturition via inhibition of spinobulbar reflexes.[16] The anticholinergic effects of antipsychotics may also have a role.

The association between antipsychotic drug use and different infections (pneumonia, UTIs) suggests that these drugs affect the immune system. Although psychotropic medications have been shown to modulate immune activation, the effects of individual psychotropic agents on the immune system and how these effects might contribute to their efficacy remain largely unclear.[17] A recent study showed that haloperidol lowered interleukin 6 and cortisol levels in healthy volunteers,[18] and interleukin 6 and cortisol have been shown to have a role in acute or chronic stress, suppressing the immune system.[18] Future research has to elucidate the mechanism of how antipsychotics are associated with UTIs.

We found that dementia was the only confounder in our analysis of all the comorbidities, which are known risk factor to influence the occurrence of UTI. Older adults with behavioral disturbances of dementia may be more susceptible to UTIs because of malnutrition, wrong wiping after urination, poor hygiene, or going to the toilet less often. In a group of younger adults with

TABLE 2. Hazard Ratio Urinary Tract Infections in Antipsychotic Users

	No. UTIs	Person Years	Crude HR (95% CI)	Age-/Sex-Adjusted HR (95% CI)	Full-Adjusted* Men and Women HR (95% CI)	Full-Adjusted* HR (95% CI)	
						Men	Women
Past use of antipsychotic	72,350	747,267	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Current use of antipsychotic	12,149	79,571	1.54 (1.51–1.57)	1.43 (1.40–1.46)	1.31 (1.28–1.34)	1.43 (1.37–1.50)	1.28 (1.25–1.31)
Analysis within current antipsychotic users							
Duration of antipsychotic use, days							
1–14	1068	6282	1.70 (1.60–1.81)	1.75 (1.65–1.86)	1.83 (1.73–1.95)	2.06 (1.82–2.33)	1.77 (1.65–1.90)
15–30	760	5049	1.51 (1.41–1.62)	1.51 (1.41–1.63)	1.53 (1.42–1.64)	1.70 (1.47–1.97)	1.48 (1.35–1.60)
31–90	1598	9484	1.68 (1.60–1.77)	1.62 (1.54–1.70)	1.59 (1.51–1.67)	1.80 (1.62–1.98)	1.53 (1.44–1.62)
>90	8723	58,756	1.51 (1.47–1.54)	1.36 (1.33–1.39)	1.20 (1.17–1.23)	1.28 (1.21–1.34)	1.19 (1.15–1.22)
Defined daily doses of antipsychotic drug[†]							
<0.125	3242	18,084	1.80 (1.74–1.87)	1.59 (1.54–1.65)	1.38 (1.32–1.43)	1.50 (1.39–1.62)	1.35 (1.29–1.41)
0.125–0.5	4607	29,576	1.60 (1.55–1.64)	1.47 (1.42–1.51)	1.30 (1.26–1.34)	1.43 (1.34–1.53)	1.27 (1.23–1.32)
>0.5	4050	31,911	1.31 (1.27–1.36)	1.27 (1.23–1.31)	1.26 (1.22–1.30)	1.36 (1.27–1.46)	1.24 (1.20–1.28)
Type of antipsychotic drug							
Atypical antipsychotics[‡]	5652	42,437	1.34 (1.30–1.37)	1.27 (1.23–1.30)	1.24 (1.21–1.28)	1.36 (1.28–1.45)	1.21 (1.18–1.25)
Typical antipsychotics[§]	6247	36,032	1.76 (1.72–1.81)	1.60 (1.56–1.64)	1.37 (1.33–1.41)	1.48 (1.28–1.45)	1.35 (1.30–1.39)
Concurrent use of more than one antipsychotic	250	1102	2.26 (1.99–2.56)	2.01 (1.78–2.28)	1.64 (1.45–1.87)	1.92 (1.50–2.48)	1.58 (1.37–1.83)

*Full adjusted for potential confounders: age, sex, recurrent UTIs, diabetes mellitus, immunosuppressive medication, stroke, urine incontinence, cognitive impairment or dementia, disability in activities of daily living, presence of a cystocele, catheterization, kidney stones or anomalies of the kidney or urinary tract, urinary retention, malignancy, radiotherapy, and surgery for prostate cancer or prostatic processes.

[†]DDD of haloperidol, for example, is 8 mg for treatment of psychosis in adults.

[‡]Clozapine, olanzapine, quetiapine, amisulpiride, sulpiride, risperidone, aripiprazole.

[§]Benperidol, chlorpromazine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, lurasidone, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sertindole, thioridazine, trifluoperazine, zotepine, zuclopentixol.

acute psychosis, UTIs occurred much more often than in healthy controls and were related to the psychosis itself.[19]

The strengths of this study are its population-based nature, the substantial sample size, and the reliable collection of longitudinal data on antipsychotic prescriptions issued by general practitioners and the diagnosis of UTI. The quality of data in English general practice is enhanced by the use of the Quality and Outcomes Framework.[7,8]

However, the study also had some limitations. The presence of UTI was based on Read codes, which can lead to misclassification. Moreover, UTI may be defined differently. We expect that general practitioners in the UK follow the Scottish Intercollegiate Guidelines Network for diagnosing UTI.[20] According to this guideline, the diagnosis of UTI is primarily based on symptoms and signs in combination with bacteria or white cells in the urine. The diagnosis of upper UTI is based on evidence of UTI, with symptoms suggestive of pyelonephritis (loin pain, flank tenderness, fever, rigor, or other manifestations of systemic inflammatory response).[20] However, older adults can present with atypical symptoms, such as confusion.[6] There was substantial misclassification in the division between complicated and uncomplicated UTI in the group of men with UTI. Of the total number of 16,055 UTI events in men, 13,932 (87%) were assigned a Read code for uncomplicated UTI, although according to the Scottish Intercollegiate Guidelines Network guidelines used in the UK, all UTIs in men should be considered complicated UTIs. Therefore, we cannot draw clear conclusions for the group of older adults with complicated UTIs, only for the whole group of older adults with UTI. However, we believe that the misclassification considers the subdivision between complicated and uncomplicated, not the diagnoses of UTI as a whole.

The cohort study we conducted compared the incidence of UTIs during periods of active, current use of antipsychotics versus periods of nonuse of antipsychotics, but all patients in the cohort started with at least an initial prescription for an antipsychotic drug. The design of the cohort study was such that it was nested within users of antipsychotic users to reduce confounding by underlying conditions not present in nonusers of antipsychotics. Hence, there were no neverusers present and we could not calculate the relative risk in current users versus never users.

Another potential limitation is underestimation of the true magnitude of the effect, because many older adults may self-treat their UTI or not go to their general practitioner for their symptoms. Furthermore, the antipsychotic prescriptions were issued by general practitioners; there were no data for prescriptions issued by medical specialists. Hence, our results may not be generalizable to those older adults. Next, we presume that patients have taken their medication as prescribed. This was not verified.

In conclusion, the use of antipsychotics was associated with an increased risk of UTIs in both older men and women, particularly in the first weeks of treatment. This relation should be recognized by doctors prescribing for older adults and by older adults themselves. In older adults, antipsychotic use should be restricted to those for whom treatment is absolutely necessary.

AUTHOR DISCLOSURE INFORMATION

All authors declare that there are no conflicts of interest.
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