Observed Association between Antidepressant Use and Pneumonia Risk Was Confounded by Comorbidity Measures

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Abstract

Objective—A prior study suggested that antidepressants might increase the risk of hospitalization for pneumonia in the elderly. This study sought to confirm or refute this hypothesis.

Study Design and Setting—Case-control study of persons age 65 and above nested in the UK General Practice Research Database.

Results—We identified 12,044 cases of the hospitalization for pneumonia (the primary outcome) and 48,176 controls. The odds ratio (OR) for any antidepressant use, adjusting for age, sex, and calendar year was 1.61 (95% confidence interval 1.46 to 1.78). After further adjustment for comorbidity measures, the OR was 0.89 (0.79 to 1.00). We also identified 159 cases of hospitalization for aspiration pneumonia (the secondary outcome) and 636 controls. The OR for any antidepressant use, adjusted for age, sex, and calendar year was 1.45 (0.65 to 3.24). After further adjustment for comorbidity measures, the OR was 0.63 (0.23 to 1.71).

Conclusion—These findings refute the prior hypothesis that use of antidepressants by elderly patients increases the risk of hospitalization for pneumonia or for aspiration pneumonia. Decisions regarding use of antidepressants in elderly persons should not be affected by concern about pneumonia risk. Data-derived hypotheses should be independently confirmed before being acted upon.

Keywords

aged; antidepressive agents; pneumonia; pneumonia, aspiration; pharmacoepidemiology

1. Introduction

Pneumonia is a major cause of morbidity and mortality in the elderly. Together with influenza, pneumonia constitutes the fifth leading cause of death in those age 65 years and older in the US, behind heart disease, cancer, stroke, and chronic lower respiratory diseases [1]. The incidence of hospitalization for pneumonia for those age 65 years and older in the US increased by 20% from 1988 to 2002 [2]. One major etiologic factor for pneumonia in the elderly is aspiration of oropharyngeal contents [3,4]. Although the clinical diagnosis of aspiration as a cause of pneumonia is often uncertain [4,5], the incidence of hospitalization for diagnosed aspiration pneumonia in US elderly nearly doubled between 1991 and 1998 [6].

A recent study undertaken to identify possible signals of iatrogenic illness in the elderly found that hospitalization for aspiration pneumonia was three times as likely to occur in the ninety-day period following a hospitalization for depression as in the ninety-day period preceding a hospitalization for depression [7], leading to the hypothesis that antidepressant drugs may increase the risk of aspiration pneumonia. If true, such an effect could have major therapeutic implications for the treatment of elderly depressed patients, since the benefit of pharmacotherapy would need to be weighed against the risk of aspiration pneumonia, a serious outcome. However, this prior study was limited in that it identified diagnoses occurring disproportionately after vs. before hospitalizations for depression in order to identify potential signals. It did not measure exposure to antidepressants or attempt to control for patient factors that may change over time.

The objective of this study was to evaluate the hypothesis that antidepressant use in the elderly is associated with hospitalization for pneumonia (our primary aim) or hospitalization for aspiration pneumonia or pneumonitis (our secondary aim).

2. Subjects and methods

2.1. Overview and study population

We performed an observational case-control study nested within the General Practice Research Database (GPRD) from the UK. GPRD data constitute the primary outpatient electronic medical records from approximately two thousand general practitioners (GPs) in the UK. Within the UK, approximately 98% of the population is registered with a GP, and virtually all patient care is coordinated by the GP through the National Health Service. The database is broadly representative of the UK population in terms of age, sex, and geography. More than 500 published epidemiologic studies have been performed using this database. The GPRD records outpatient prescriptions, outpatient diagnoses, and hospital diagnoses that are entered in response to receipt of a consultant's letter or discharge summary [8]. We used GPRD data entered from its establishment in 1987 through April 2002, and included only data classified as "up-to-standard" for identifying exposures and outcomes [8].

2.2 Study base

The person-time eligible for inclusion in this nested case-control study (i.e., the study base within which the case-control study was nested) was all up-to-standard person-time occurring in individuals age 65 years and above with at least six months of prior up-to-standard follow-up in whom no instance of the study outcome had yet occurred. We required at least six months

of data prior to study eligibility to ensure an adequate period in which to measure baseline variables. Cases and controls were sampled from this study base using incidence density sampling, as described below, which results in odds ratios (ORs) that are interpretable as incidence rate ratios [9].

2.3 Identification of cases

Cases of the primary outcome consisted of all individuals who were hospitalized with pneumonia at any time following the six month anniversary date of that person's up-to-standard entry date. Cases of the secondary outcome consisted of persons who were hospitalized with aspiration pneumonia or aspiration pneumonitis at any time following the six month anniversary date of that person's up-to-standard entry date. The index date for cases was the date of the case event. For persons with more than one case event, we included only the first event. Diagnostic codes for the study outcomes are listed in the Appendix.

2.4 Identification of controls

For each case, we randomly selected four controls from the same GP practice using incidence density sampling [9] based on amount of time in the study base. In particular, potential controls were persons who contributed person-time to the study base (defined above), who had not yet experienced the relevant study outcome before the corresponding case's event, assessed with respect to entry into the study base. The index date for controls was defined as the date of entry into the study base plus the number of days of event-free follow-up contributed by the corresponding case. This is analogous to time-to-event analyses of cohort studies, and ensures the interpretability of the resulting odds ratios as incidence rate ratios [9].

2.5 Ascertainment of exposure

The principal exposure definition was a recorded prescription for any antidepressant medication in the thirty days preceding the index date. Prescriptions for chronically administered medications in the UK are issued in one-month increments. In order to obtain repeat prescriptions (i.e., prescription refills), patients must telephone or visit the GP office, which then issues and records a repeat prescription. To confirm the tendency to provide a one-month supply per prescription, we examined the frequency distribution of the number of days between subsequent prescriptions for commonly used antidepressants for the same patient. There was a very strong central tendency (i.e., mode and median) for repeat prescriptions to be issued approximately every thirty days (data not shown). In addition to considering exposure to any antidepressant, we also performed sub-analyses of the two major subclasses: cyclic agents (amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dibenzepin, dosulepin, doxepin, imipramine, iprindole, lofepramine, maprotiline, mianserin, mirtazapine, nortriptyline, opipramol, protriptyline, trimipramine) and selective serotonin uptake inhibitors and selective serotonin and norepinephrine inhibitors (SSRI/SSNRIs; citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, zimeldine).

2.6 Ascertainment of potential confounding factors

Potential confounding factors were ascertained based on the index date. These are listed in Table 1 and Table 2, and included demographic factors, diagnoses ever recorded in the past (focusing on conditions previously implicated as risk factors for pneumonia, including chronic neurologic and pulmonary conditions [4]), drug prescribed ever in the past (as markers of disease), currently prescribed drugs (i.e., within the past thirty days), and measures of morbidity and health care utilization (e.g., number of non-antidepressant prescriptions in the prior thirty days, number of GP visits for non-depression diagnoses in the prior thirty days, number of hospitalizations in the prior six months).

2.7 Statistical analysis

We first compared cases to controls with respect to antidepressant exposure and potential confounding factors. We next used conditional logistic regression to fit a "minimally adjusted" model that estimated the odd ratio (OR) for antidepressant use adjusting for age (expressed as a continuous variable), sex, and calendar year (to account for potential secular trends in pneumonia hospitalization and antidepressant use). We then examined each potential confounding factor individually using a change-in-estimate criterion [10]. In particular, we individually added each potential confounding factor to the minimally adjusted model. If any factor changed the OR of interest by ten percent or more, we considered it to be a confounding factor and retained it in the "change-in-estimate" adjusted model. We used this same strategy to examine the association with each antidepressant subclass. However, because of the small number of events of the secondary outcome (aspiration pneumonia), we were unable to examine associations for this outcome with specific antidepressant subclasses. We used SAS version 9.1 for all analyses.

The incidence of pneumonia is expected to peak during the winter months and decline during the summer, whereas antidepressant therapy might be prescribed year-round. We compared the seasonal distribution of hospitalization for pneumonia in patients with and without exposure to antidepressants using the method of Edwards [11]. This sums the vectors for the number of cases in each month extending from a common origin to the midpoints of twelve equal sectors of a circle from January (0 to 30°) through December (330 to 360°).

Based on pilot data, our *a priori* power calculations suggested that using a two-tailed α of 5%, we would have 85% statistical power to detect an OR for exposure to any antidepressant of 1.07 or higher for pneumonia hospitalization, and an OR of 1.5 or higher for hospitalization for aspiration pneumonia or pneumonitis [12].

3. Results

3.1. Primary outcome: hospitalization for pneumonia

We identified 12,044 cases of hospitalization for pneumonia. For each case, we identified four controls, for a total of 48,176 controls. Table 1 presents a comparison of cases and controls for the primary outcome. Cases were older than controls (median age 81 vs. 75), and had a substantially higher number of non-depression GP visits in the prior six months (average 2.8 vs. 0.8), hospital visits over the prior six months (mean 0.72 vs. 0.13), and number of non-antidepressant prescriptions in the prior month (mean 3.6 vs. 2.0). Most diagnoses, drugs prescribed ever in the past, and currently prescribed drugs examined were substantially more common among cases than controls (Table 1).

The OR (95% CI) for the association between pneumonia hospitalization and any antidepressant use, adjusted for age, sex, and calendar year (i.e., the minimally adjusted model) was 1.61 (1.46 to 1.78). However, when further adjusting for factors in Table 1 that changed the OR by ten percent or more (number of non-depression GP visits in the prior six months, ever past benzodiazepine prescription, and ever past antipsychotic prescription) the OR (95% CI) was 0.89 (0.79 to 1.00) (Table 1).

In the analysis of the major antidepressant subclasses, the ORs for cyclic antidepressants, SSRIs/SSNRIs, and other agents were similar to the corresponding OR for any antidepressant in baseline model (Table 1). The change-in-estimate adjusted ORs for cyclic agents and SSRI/SSNRIs were also similar to the corresponding OR for antidepressants as a whole (Table 1).

The seasonal vector of hospitalization for pneumonia in patients without prescriptions for antidepressants showed the expected pronounced wintertime peak (0.088 units at 27°, i.e., late

January). This vector was closely matched in both relative amplitude and direction (0.103 units at 23°) by that of hospitalization for pneumonia in patients who were receiving antidepressants (data not shown).

3.2 Secondary outcome: hospitalization for aspiration pneumonia or aspiration pneumonitis

We identified 159 cases of hospitalization for diagnosed aspiration pneumonia or pneumonitis, and 636 controls. Table 2 presents a comparison of cases and controls for the secondary outcome. The relationships of the factors presented in Table 2 with hospitalization for aspiration pneumonia or pneumonitis were similar to those seen for the primary outcome, although the confidence intervals are much wider in Table 2 because of the small number of events. The OR (95% CI) for any antidepressant use, adjusted for age, sex, and calendar year was 1.45 (0.65 to 3.24). When further adjusting for factors in Table 2 that changed the OR by ten percent or more (number of non-depression GP visits in the prior six months, ever past benzodiazepine prescription, and ever past antipsychotic prescription) the OR (95% CI) was 0.63 (0.23 to 1.71) (Table 2). There were not enough users of specific antidepressant subclasses with this outcome to analyze these subclasses separately.

4. Discussion

The purpose of this study was to further evaluate the hypothesis that antidepressants may increase the risk of hospitalization for aspiration pneumonia in the elderly [7]. This signal arose in the context of a systematic process to screen for iatrogenic factors that may lead to depression, and for complications of depression treatment. The positive association that we observed between antidepressants and pneumonia hospitalization, the primary outcome, before adjusting for clinical variables, is consistent with, but somewhat lower than (1.6 vs. 3.0) the earlier signal that hospitalization for aspiration pneumonia in the elderly is more common after than before a hospitalization for depression. In other words, pneumonia hospitalization does indeed seem to be more common in antidepressant users. However, the earlier study [7] screened administrative claims data with the goal of identifying a potential wide range of potential signals to be further tested, did not measure actual exposure to antidepressant drugs, and made no attempt to control for patient factors that may change over time. In contrast, the current study focused on examining a particular association, with an emphasis on controlling for confounding.

The results of this study are reassuring that, once comorbidity measures are taken into account, there is no evidence that antidepressants increase the risk of hospitalization for pneumonia in the elderly. This is true for the general class of antidepressants and specifically for cyclic agents and SSRIs/SSNRIs. This conclusion is reinforced by the observation that the occurrence of pneumonia in patients prescribed antidepressants did not deviate from the expected wintertime peak in incidence. In addition to following up a potential signal, and in the process providing reassurance about the safety of antidepressants with regard to pneumonia in the elderly, this study confirms earlier findings that increasing age and the presence of comorbidities are strongly associated with pneumonia [13–17].

This study has limitations. Although the GPRD is derived from the primary medical record, and diagnoses recorded in the GPRD are generally regarded as being of high quality [8], these study outcomes have not been specifically validated. However, misclassification of the outcome seems unlikely to be responsible for our negative findings because there was a positive association between antidepressants and pneumonia in the minimally adjusted analysis. In addition, we did confirm associations with pulmonary and neurologic conditions, and other factors that would be expected to be associated with pneumonia. Exposure misclassification could also have played a role, in that patients prescribed antidepressant drugs might not take them, which could have tended to produce bias toward the null. However, exposure

misclassification would have resulted in bias toward the null in both the unadjusted and adjusted analyses. Because of the large number of cases of hospitalization for depression, and the narrow CIs for this effect estimate, type-2 error is unlikely to have played a prominent role in the primary outcome. However, as we recognized at the outset, type-2 error is more of a concern for the secondary outcome.

In conclusion, we performed a controlled epidemiologic study to follow up on a prior data-derived hypothesis that, if true, could have had important therapeutic implications for elderly patients with depression. Although there was indeed an unadjusted association between antidepressant medication use and pneumonia hospitalization, the observed association appeared to be due to confounding by measured co-morbidity measures. This reinforces the need to independently confirm data-derived hypotheses before acting on them.

Appendix

Codes used to identify community-acquired Pneumonia.

Code	Description
AyuKA00	KLEBSIELLA PNEUMONIAE/CAUSE/DISEASE CLASSIFD/OTH CHAPTERS
AyuK900	MYCOPLASMA PNEUMONIAE [PPLO]CAUSE/DIS CLASSIFD/OTH CHAPTR
Hyu0A00	OTHER BACTERIAL PNEUMONIA
Hyu0H00	OTHER PNEUMONIA, ORGANISM UNSPECIFIED
Hyu0900	PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
Hyu0B00	PNEUMONIA DUE TO OTHER SPECIFIED INFECTIOUS ORGANISMS
Hyu0C00	PNEUMONIA IN BACTERIAL DISEASES CLASSIFIED ELSEWHERE
AyuK300	STREPTOCOC PNEUMON/CAUSE/DISEASE CLASSIFIED/OTH CHAPTERS
H530300	ABSCESS OF LUNG WITH PNEUMONIA
H470312	ASPIRATION PNEUMONIA DUE TO VOMIT
H28..00	ATYPICAL PNEUMONIA
H22z.00	BACTERIAL PNEUMONIA NOS
H261.00	BASAL PNEUMONIA DUE TO UNSPECIFIED ORGANISM
485	BRONCHOPNEUMONIA
H25..00	BRONCHOPNEUMONIA DUE TO UNSPECIFIED ORGANISM
H270.11	CHEST INFECTION - INFLUENZA WITH PNEUMONIA
H22..11	CHEST INFECTION - OTHER BACTERIAL PNEUMONIA
H26..11	CHEST INFECTION - PNEMONIA DUE TO UNSPECIFIED ORGANISM
H21..11	CHEST INFECTION - PNEUMOCOCCAL PNEUMONIA
H23..11	CHEST INFECTION - PNEUMONIA ORGANISM OS
H25..11	CHEST INFECTION - UNSPECIFIED BRONCHOPNEUMONIA
H24..11	CHEST INFECTION WITH INFECTIOUS DISEASE EC
H233.00	CHLAMYDIAL PNEUMONIA
H22y011	E.COLI PNEUMONIA
H540100	HYPOSTATIC BRONCHOPNEUMONIA
H540000	HYPOSTATIC PNEUMONIA
H56y100	INTERSTITIAL PNEUMONIA
A3BXB00	KLEBSIELLA PNEUMONIAE/CAUSE/DISEASE CLASSIFD/OTH CHAPTERS
H21..00	LOBAR (PNEUMOCOCCAL) PNEUMONIA
481 B	LOBAR PNEUMONIA
H260.00	LOBAR PNEUMONIA DUE TO UNSPECIFIED ORGANISM
A3BXA00	MYCOPLASMA PNEUMONIAE [PPLO] CAUSE/DIS CLASSIFD/OTH CHAPTR
SP13100	OTHER ASPIRATION PNEUMONIA AS A COMPLICATION OF CARE
H22..00	OTHER BACTERIAL PNEUMONIA
H2y..00	OTHER SPECIFIED PNEUMONIA OR INFLUENZA
A3By400	PLEUROPNEUMONIA-LIKE ORGANISM (PPLO) INFECTION
486	PNEUMONIA
H22y200	PNEUMONIA - LEGIONELLA
486 AP	PNEUMONIA ASPIRATION
483 AT	PNEUMONIA ATYPICAL
481 BA	PNEUMONIA BASAL

Codes used to identify community-acquired Pneumonia.

Code	Description
486 CA	PNEUMONIA COLD AGGLUTININ POSITIVE
H22yz00	PNEUMONIA DUE TO BACTERIA NOS
H230.00	PNEUMONIA DUE TO EATON'S AGENT
H22y000	PNEUMONIA DUE TO ESCHERICHIA COLI
H222.11	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
H222.00	PNEUMONIA DUE TO HAEMOPHILUS INFLUENZAE
H220.00	PNEUMONIA DUE TO KLEBSIELLA PNEUMONIAE
H231.00	PNEUMONIA DUE TO MYCOPLASMA PNEUMONIAE
H22yX00	PNEUMONIA DUE TO OTHER AEROBIC GRAM-NEGATIVE BACTERIA
H22y.00	PNEUMONIA DUE TO OTHER SPECIFIED BACTERIA
H23..00	PNEUMONIA DUE TO OTHER SPECIFIED ORGANISMS
H232.00	PNEUMONIA DUE TO PLEUROPNEUMONIA LIKE ORGANISMS
H22y100	PNEUMONIA DUE TO PROTEUS
H221.00	PNEUMONIA DUE TO PSEUDOMONAS
H23z.00	PNEUMONIA DUE TO SPECIFIED ORGANISM NOS
H224.00	PNEUMONIA DUE TO STAPHYLOCOCCUS
H223.00	PNEUMONIA DUE TO STREPTOCOCCUS
H223000	PNEUMONIA DUE TO STREPTOCOCCUS, GROUP B
H26..00	PNEUMONIA DUE TO UNSPECIFIED ORGANISM
483 E	PNEUMONIA EATON'S AGENT
514 HP	PNEUMONIA HYPOSTATIC
4820K	PNEUMONIA KLEBSIELLA
483 M	PNEUMONIA MYCOPLASMAL
7789AP	PNEUMONIA NEWBORN ASPIRATION
H2z..00	PNEUMONIA OR INFLUENZA NOS
481 A	PNEUMONIA PNEUMOCOCCAL
483 AP	PNEUMONIA PRIMARY ATYPICAL
4823	PNEUMONIA STAPHYLOCOCCAL
H24..00	PNEUMONIA WITH INFECTIOUS DISEASES EC
H24z.00	PNEUMONIA WITH INFECTIOUS DISEASES EC NOS
H24y.00	PNEUMONIA WITH OTHER INFECTIOUS DISEASES EC
H24yz00	PNEUMONIA WITH OTHER INFECTIOUS DISEASES EC NOS
H243.11	PNEUMONIA WITH PERTUSSIS
H24y400	PNEUMONIA WITH SALMONELLOSIS
H243.00	PNEUMONIA WITH WHOOPING COUGH
A022200	SALMONELLA PNEUMONIA
A3BX400	STREPTOCOC PNEUMON/CAUSE/DISEASE CLASSIFIED/OTH CHAPTERS

Codes used to identify community-acquired aspiration pneumonia or pneumonitis

Code	Description
Hyu4700	[X]PNEUMONITIS DUE TO INHALATION OF OTHER SOLIDS AND LIQUIDS
H470312	ASPIRATION PNEUMONIA DUE TO VOMIT
H47..11	ASPIRATION PNEUMONITIS
SP13100	OTHER ASPIRATION PNEUMONIA AS A COMPLICATION OF CARE
486 AP	PNEUMONIA ASPIRATION
H470.00	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS
H470z00	PNEUMONITIS DUE TO INHALATION OF FOOD OR VOMITUS NOS
H470100	PNEUMONITIS DUE TO INHALATION OF GASTRIC SECRETIONS
H47y.00	PNEUMONITIS DUE TO INHALATION OF OTHER SOLID OR LIQUID
H470000	PNEUMONITIS DUE TO INHALATION OF REGURGITATED FOOD
H47z.00	PNEUMONITIS DUE TO INHALATION OF SOLID OR LIQUID NOS [Same
H47yz00	PNEUMONITIS DUE TO INHALATION OF SOLID OR LIQUID NOS OK?]
H47..00	PNEUMONITIS DUE TO INHALATION OF SOLIDS OR LIQUIDS
H470300	PNEUMONITIS DUE TO INHALATION OF VOMITUS
H470311	VOMIT INHALATION PNEUMONITIS

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Table 1.

Characteristics of cases and controls of hospitalization for pneumonia

	Cases (N = 12,044)	Controls (N = 48,176)		
median age in years (interquartile range)	81 (74 to 86)	75 (70 to 81)		
mean (SD) number of GP non-depression visits in prior six months	2.8 (3.1)	0.8 (1.6)		
mean (SD) number of non-antidepressant prescriptions in prior month	3.6 (4.1)	2.0 (2.9)		
mean (SD) number of hospital visits over prior six months	0.72 (1.13)	0.13 (0.49)		
	N (%)	N (%)	Minimally adjusted OR (95% CI)[*]	Change-in-estimate adjusted OR (95% CI)[†]
male sex	5836 (48.5)	18484 (40.4)	1.71 (1.63 to 1.78)	
alcohol use	2882 (23.9)	15846 (32.9)	0.71 (0.68 to 0.75)	
current smoking	3079 (25.6)	10915 (22.7)	1.57 (1.49 to 1.65)	
diagnoses ever in past				
Anterior horn motor neuron disease	30 (0.3)	20 (0.04)	7.29 (3.95 to 13.47)	
Anxiety	1433 (11.9)	5099 (10.6)	1.30 (1.22 to 1.39)	
bipolar disorder	33 (0.3)	76 (0.2)	2.50 (1.61 to 3.88)	
Chronic obstructive pulmonary disease	2436 (20.2)	2992 (6.2)	3.92 (3.67 to 4.18)	
cerebrovascular disease	2096 (17.4)	3829 (8.0)	2.04 (1.91 to 2.17)	
depression	2438 (20.2)	6730 (14.0)	1.75 (1.65 to 1.86)	
dysphagia	454 (3.8)	881 (1.8)	2.10 (1.85 to 2.38)	
Herpetic neuralgia / herpes zoster	916 (7.6)	3243 (6.7)	1.15 (1.06 to 1.25)	
insomnia	2712 (22.5)	7083 (14.7)	1.55 (1.46 to 1.63)	
Parkinson's disease	220 (1.8)	355 (0.7)	1.82 (1.52 to 2.19)	
poor nutritional status	120 (1.0)	153 (0.3)	2.84 (2.18 to 3.70)	
schizophrenic disorders	64 (0.5)	220 (0.5)	1.49 (1.11 to 2.00)	
senile dementia	536 (4.5)	636 (1.3)	2.24 (1.97 to 2.54)	
Suicidal ideation	7 (0.1)	19 (0.0)	1.98 (0.78 to 5.07)	
drugs prescribed ever in past				
anti-parkinsonian	551 (4.6)	842 (1.8)	2.24 (1.99 to 2.53)	
antipsychotic	3394 (28.2)	9233 (19.2)	1.59 (1.51 to 1.67)	
barbiturate	97 (0.8)	208 (0.4)	1.73 (1.33 to 2.24)	
benzodiazepine	3974 (33.0)	10300 (21.4)	1.79 (1.71 to 1.88)	
histamine H-2 receptor antagonist	2844 (23.6)	8162 (16.9)	1.60 (1.51 to 1.68)	
mood stabilizer	49 (0.4)	131 (0.3)	1.91 (1.35 to 2.71)	
Opiate	2760 (22.9)	7072 (14.7)	1.93 (1.83 to 2.04)	
proton pump inhibitor	1251 (10.4)	3584 (7.4)	1.68 (1.56 to 1.81)	
currently prescribed drugs				
antidepressant	687 (5.7)	1643 (3.4)	1.61 (1.46 to 1.78)	0.89 (0.79 to 1.00)[‡]
cyclic	487 (4.04)	1198 (2.49)	1.57 (1.40 to 1.77)	0.92 (0.80 to 1.05)[§]
SSRI/SSNRI	183 (1.52)	399 (0.83)	1.65 (1.36 to 1.99)	0.86 (0.69 to 1.07)[§]
anti-parkinsonian	215 (1.8)	430 (0.9)	1.61 (1.35 to 1.92)	
antipsychotic	736 (6.1)	1290 (2.7)	1.82 (1.64 to 2.02)	
barbiturate	46 (0.4)	102 (0.2)	1.64 (1.13 to 2.38)	
benzodiazepine	1377 (11.4)	3265 (6.8)	1.55 (1.44 to 1.67)	
histamine H-2 receptor antagonist	651 (5.4)	1749 (3.6)	1.37 (1.25 to 1.52)	
mood stabilizer	17 (0.1)	60 (0.1)	1.19 (0.68 to 2.09)	
opiate	576 (4.8)	740 (1.5)	3.29 (2.91 to 3.71)	
proton pump inhibitor	437 (3.6)	1104 (2.3)	1.76 (1.55 to 1.99)	

[*] Adjusted for age, sex, calendar year, and current use of an antidepressant drug

[†] Adjusted for age, sex, calendar year, and any factor in Table 1 that changed the OR for exposure by ten percent or more.

[‡] Adjusted for age, sex, calendar year, number of non-depression GP visits in the prior six months, ever past benzodiazepine prescription, and ever past antipsychotic prescription

[§] Adjusted for age, sex, calendar year, number of non-depression GP visits in prior six months, number of non-antidepressant prescriptions in the prior month, ever past benzodiazepine prescription, and ever past antipsychotic prescription

SD denotes standard deviation

GP denotes general practitioner

OR denotes matched odds ratio

CI denotes confidence interval

SSRI/SSNRI denotes selective serotonin reuptake inhibitor / selective serotonin and norepinephrine reuptake inhibitor

Table 2.

Characteristics of cases and controls of hospitalization for aspiration pneumonia or aspiration pneumonitis

	Cases (N = 159)	Controls (N = 636)		
median age in years (interquartile range)	80 (75 to 86)	77 (72 to 82)		
mean (SD) number of GP non-depression visits in prior six months	3.16 (3.03)	0.84 (1.65)		
mean (SD) number of non-antidepressant prescriptions in prior month	4.09 (5.02)	2.33 (3.20)		
mean (SD) number of hospital visits over prior six months	1.09 (1.38)	0.15 (0.61)		
	N (%)	N (%)	Minimally Adjusted OR (95% CI)[*]	Change-in-estimate adjusted OR (95% CI)[†]
male sex	84 (52.8)	211 (36.0)	2.57 (1.72 to 3.84)	
alcohol use	44 (27.7)	204 (32.1)	0.70 (0.44 to 1.11)	
smoking	40 (25.2)	146 (23.0)	1.22 (0.76 to 1.97))	
diagnoses ever in past				
anterior horn motor neuron disease	4 (2.5)	0 (0.0)	inestimable	
anxiety	22 (13.8)	77 (12.1)	1.43 (0.82 to 2.48)	
bipolar disorder	0 (0.0)	2 (.03)	inestimable	
chronic obstructive pulmonary disease	29 (18.2)	47 (7.4)	2.91 (1.66 to 5.09)	
cerebrovascular disease	65 (40.9)	69 (10.9)	5.64 (3.51 to 9.05)	
depression	35 (22.0)	101 (15.9)	1.74 (1.03 to 2.95)	
dysphagia	27 (17.0)	8 (1.3)	23.11 (8.30 to 64.36))	
herpetic neuralgia / herpes zoster	17 (10.7)	49 (7.7)	1.77 (0.93 to 3.37)	
insomnia	35 (22.0)	126 (19.8)	1.27 (0.78 to 2.08)	
Parkinson's disease	6 (3.8)	4 (0.6)	6.91 (1.69 to 28.3)	
poor nutritional status	7 (4.4)	2 (0.3)	13.92 (2.67 to 72.69)	
schizophrenic disorders	2 (1.3)	1 (0.2)	30.42 (2.19 to 423.2)	
senile dementia	11 (6.9)	9 (1.4)	3.39 (1.26 to 9.10)	
suicidal ideation	1 (0.6)	1 (0.2)	10.01 (0.49 to 205.8)	
drugs prescribed ever in past				
antipsychotic	57 (35.9)	141 (22.2)	2.04 (1.33 to 3.14)	
anti-parkinsonian	15 (9.4)	6 (0.9)	10.81 (3.72 to 31.42)	
barbiturate	2 (1.3)	6 (0.9)	2.32 (0.39 to 13.95)	
benzodiazepine	54 (34.0)	163 (25.6)	1.91 (1.25 to 2.93)	
histamine H-2 receptor antagonist	45 (28.3)	131 (20.6)	1.56 (1.02 to 2.39)	
mood stabilizer	4 (2.5)	2 (0.3)	4.56 (0.74 to 28.24)	
opiate	39 (24.5)	116 (18.2)	1.89 (1.18 to 3.03)	
proton pump inhibitor	31 (19.5)	57 (9.0)	2.55 (1.48 to 4.38)	
currently prescribed drugs				
antidepressant	11 (6.9)	28 (4.4)	1.45 (0.65 to 3.24)	0.63 (0.23 to 1.71)[‡]
cyclic	6 (3.8)	23 (3.6)		
SSRI/SSNRI	4 (2.5)	5 (0.8)		
antipsychotic	12 (7.6)	25 (3.9)	1.43 (0.64 to 3.22)	
anti-parkinsonian	5 (3.1)	2 (0.3)	6.16 (1.09 to 34.81)	
barbiturate	1 (0.6)	3 (0.5)	3.07 (0.22 to 42.11)	
benzodiazepine	12 (7.6)	25 (3.9)	0.88 (0.43 to 1.80)	
histamine H-2 receptor antagonist	7 (4.4)	25 (3.9)	1.00 (0.39 to 2.54)	
mood stabilizer	1 (0.6)	0 (0.0)	inestimable	
opiate	4 (2.5)	18 (2.8)	1.20 (0.37 to 3.87)	
proton pump inhibitor	11 (6.9)	14 (2.2)	3.12 (1.24 to 7.85)	

[*] Adjusted for age, sex, calendar year, and current use of an antidepressant drug

[†] Adjusted for age, sex, calendar year, and any factor in Table 1 that changed the OR for exposure by ten percent or more.

[‡] Adjusted for age, sex, calendar year, chronic obstructive pulmonary disease, dysphagia, senile dementia, ever past antipsychotic prescription, ever past benzodiazepine prescription, and current anti-parkinsonian agent

SD denotes standard deviation

GP denotes general practitioner

OR denotes matched odds ratio

CI denotes confidence interval

SSRI/SSNRI denotes selective serotonin reuptake inhibitor / selective serotonin and norepinephrine reuptake inhibitor