

# Pneumonia following antipsychotic prescriptions in electronic health records: a patient safety concern?

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## ABSTRACT

### Background

In screening the Intercontinental Medical Statistics (IMS) Health Disease Analyzer database of GP records from the UK, an increased registration of pneumonia subsequent to the prescription of some antipsychotic medicines was identified.

### Aim

To investigate the temporal pattern between antipsychotic prescriptions and pneumonia with respect to age, type of pneumonia and other chest infections, and antipsychotic class.

### Design of study

Self-controlled cohort analysis.

### Setting

Electronic health records from the UK IMS Health Disease Analyzer database.

### Method

Three groups of pneumonia-related International Classification of Diseases (ICD)-10 terms and prescriptions of atypical and conventional antipsychotic medicines were studied. Separate analyses were carried out for patients aged  $\geq 65$  years. The observed rate of pneumonia terms registered in different time periods in connection to antipsychotic prescriptions was contrasted to the overall rate of pneumonia terms relative to prescriptions of other drugs in the same dataset.

### Results

In patients aged  $\geq 65$  years, an increased registration of a group of terms defined as 'acute chest infections', after atypical antipsychotic prescriptions, was identified. The corresponding increase after conventional antipsychotic prescriptions was much smaller. Bronchopneumonia had a striking increase after both atypical and conventional antipsychotic prescriptions, and was commonly recorded with fatal outcome. Few registrations of hypostatic pneumonia were noted. Patients aged  $< 65$  years did not have a higher rate of acute chest infections after receiving antipsychotic prescriptions.

### Conclusion

The consistent pattern of an increased rate of chest infections after atypical antipsychotic prescriptions in older people seen in this outpatient study, together with the higher risk shown in a previous study on hospitalised patients, suggests a causal relationship. This is of importance since bronchopneumonia seems highly linked to fatal outcome. In the absence of a mechanism, further investigation of the role of antipsychotics in older people is needed.

### Keywords

aged; antipsychotic agents; computerised medical records systems; pneumonia.

## INTRODUCTION

Pneumonia can result in serious consequences, particularly in patients who are old and frail. The higher risk of death in older patients with dementia using antipsychotic medicines,<sup>1-2</sup> shown in meta-analyses on placebo-controlled studies was, apart from heart-related events, due to infections such as pneumonia.<sup>1,3</sup> These publications did not reveal details of pneumonia rates, comparing antipsychotic and placebo treatments.

Infections (mostly pneumonia) were the reason for non-cancer mortality in 10% of new users of antipsychotics in a large database cohort study on older people and, compared with users of atypical antipsychotics, the group using conventional antipsychotics showed a higher incidence (although not statistically significant) of pneumonia-related

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mortality.<sup>4</sup> A US study of users of antipsychotics who were admitted to the hospital for pneumonia showed a higher mortality rate for those who used conventional, rather than atypical, antipsychotics.<sup>5</sup> Antipsychotic use — in the case of the conventional group — among patients with Alzheimer's disease has shown to be a risk factor for aspiration pneumonia due to a noted drug effect on the swallowing reflex.<sup>6</sup>

Older patients currently using antipsychotic medicines, when compared with those not currently using them, were noted to be at higher risk for pneumonia with an adjusted odds ratio of 1.6 (95% confidence interval [CI] = 1.3 to 2.1) in a nested case control study on pharmacy dispensing and hospital discharge registrations.<sup>7</sup> Users of atypical antipsychotics showed a higher risk for pneumonia than users of conventional antipsychotics.

In prescribing information of antipsychotic drugs,<sup>8</sup> pneumonia is most often described in connection with the increased risk of death in older people with dementia, or listed as aspiration pneumonia. Further details of pneumonia in association to antipsychotic use are limited.

When screening the Intercontinental Medical Statistics (IMS) Health Disease Analyzer database of GP records from the UK, a finding that pneumonia was registered more frequently than expected after the introduction of risperidone prompted further investigation of the temporal pattern between any antipsychotic drug prescription and pneumonia-related terms, particularly in patients aged  $\geq 65$  years.

## METHOD

The UK IMS Health Disease Analyzer dataset used contained information of prescriptions and medical records of more than 2 million patients from different GP practices in the UK. Medical problems and notes are coded on entry by the GP using Read Codes. These Read Codes are mapped by IMS Health to the International Classification of Diseases (ICD)-10 terminology and defined in this analysis as 'medical events'. Data quality is maintained by the presence of data-quality markers in the database; collated information from the markers is used to feed back to GPs, which helps maintain and improve data quality in the database.<sup>9</sup>

The pattern-discovery method for longitudinal patient records, previously described in Norén *et al*,<sup>10</sup> was applied on the UK IMS Health Disease Analyzer dataset as of 1 January 2006. The method contrasts the observed rate of registration of a medical event (here a pneumonia-related ICD-10 term) in various time periods relative to the prescription of a drug (here antipsychotics), to the overall registration rate of the same medical event, relative to prescriptions

## How this fits in

A previous study showed an increased risk of pneumonia in older patients currently using antipsychotic drugs in the Netherlands, based on prescription data and hospital discharge records. The current analysis offers a unique possibility to view patterns in records of pneumonia and other chest infections, both before and after antipsychotics were prescribed, in outpatient general practice. In patients aged  $\geq 65$  years, an increased registration of chest infections subsequent to the prescription of atypical antipsychotics was noted, relative to the rate in the same patients preceding the prescription.

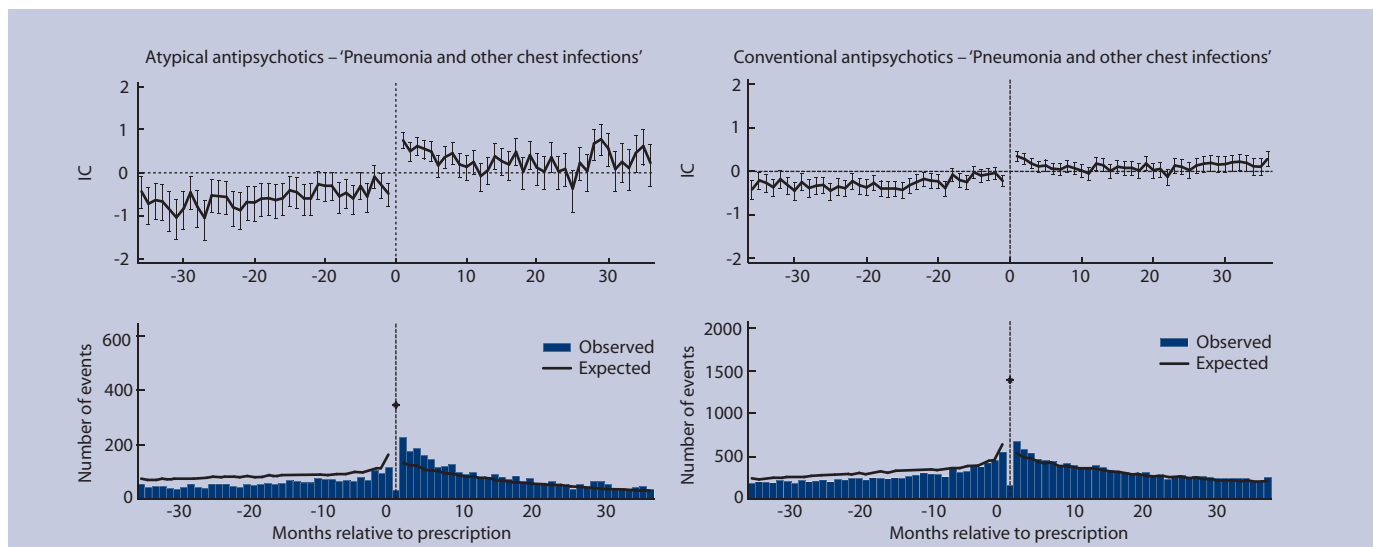
of other drugs in the same data. For each time period of interest (the results presented are for monthly intervals), a measure of association — referred to as the Information Component (IC) — is computed. This indicates whether the medical event is registered unexpectedly frequently ( $IC > 0$ ), unexpectedly rarely ( $IC < 0$ ) or as often as can be expected ( $IC = 0$ ) in a given time period, based on the overall registration rate for the event relative to other drugs.

A graphical representation of the IC values, along with observed and expected numbers of events in different time periods, provides an overview of the temporal relationship between two events; this is referred to as a chronograph. To screen for patterns of temporal association, an  $IC_{\Delta}$  value is computed that contrasts the IC value in the month immediately after a prescription with the IC value in a 6-month control period centred 2 years prior. For both IC and  $IC_{\Delta}$ , a combination of statistical shrinkage and uncertainty intervals is used to reduce the risk of highlighting spurious associations. The lower limit of the 95% credibility interval is referred to as  $IC_{0.025}$  for the IC and as  $IC_{\Delta 0.025}$  for  $IC_{\Delta}$ .

To avoid dominance of repeat prescriptions, the analysis was restricted to new prescriptions of the antipsychotic medicine, defined as the first record of the drug prescription over a course of 13 months. Drugs within the European Pharmaceutical Market Research Association's anatomical classification of pharmaceutical products<sup>11</sup> — the atypical (N05A1) and conventional antipsychotic (N05A9) groups — were used. The pneumonia-related ICD-10 terms were grouped and will be referred to in this article as follows:

- 'acute chest infections' (ICD codes J110, J12x-16x, J181, 188, 189, J220);
- bronchopneumonia (J180); and
- 'hypostatic pneumonia' (J182, J69x).

The acute chest infections group was defined as being rather inclusive, for example, as for 'unspecified acute lower respiratory infection' (J220). Graphs labelled 'pneumonia and other chest infections' include all ICD-10 terms used in this study.



**Figure 1. Chronographs for records of 'pneumonia and other chest infections' relative to atypical and conventional antipsychotic prescriptions for all ages. IC value on the day (month = 0) for the IC graph was below -2 and outside the scale.**

Appendices 1, 2 and 3 give a complete listing of all the ICD-10 codes with the names specified, as well as the linked Read Codes within each group of ICD-10 codes that were used in the search. The age groups used were 18–64 years and  $\geq 65$  years.

Details of the patients linked with pneumonia-related terms that were recorded within the month after an atypical or conventional antipsychotic prescription were also reviewed.

## RESULTS

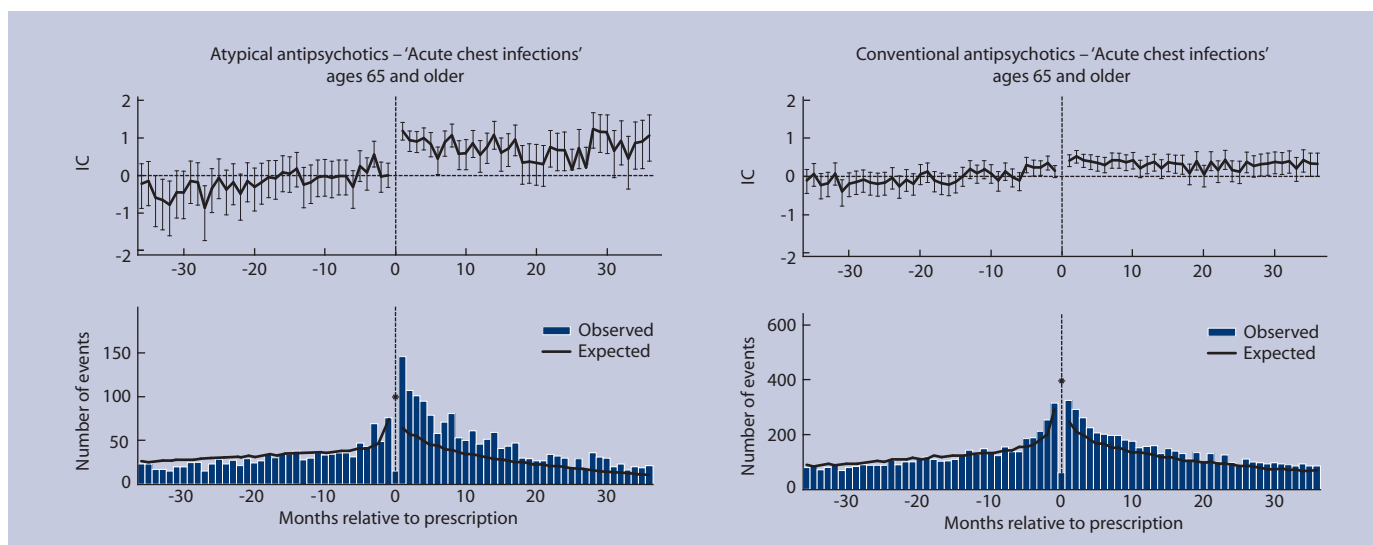
### *Pneumonia and other chest infections over time: chronographs*

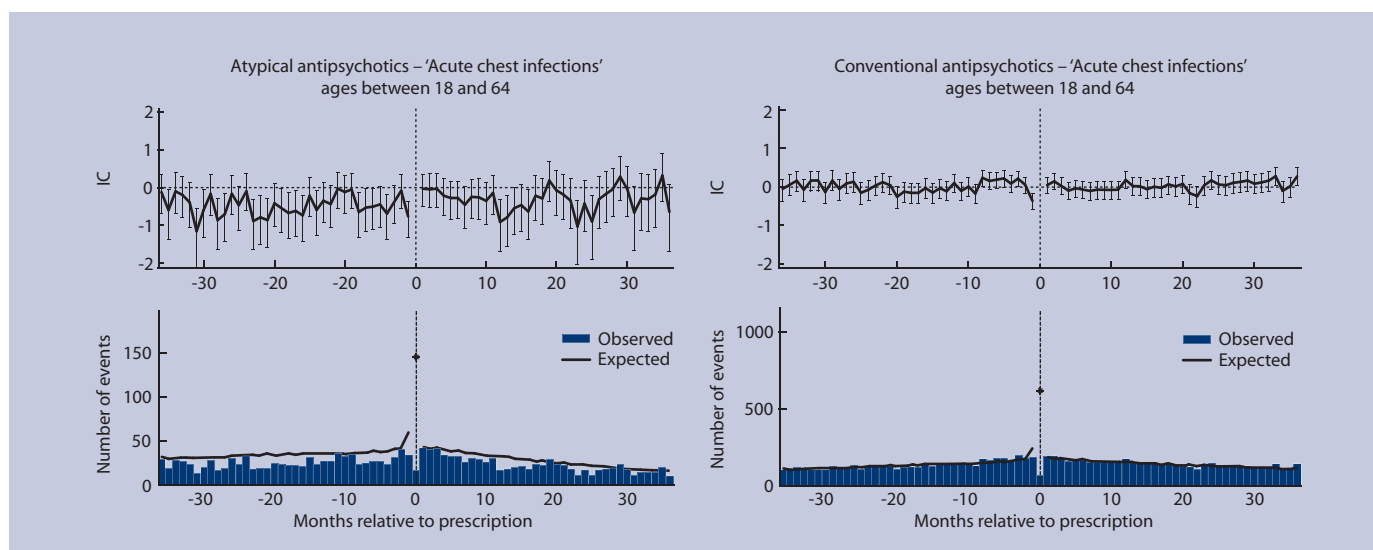
The figures with chronographs display monthly registrations of the different pneumonia-related term groupings, 3 years before and after atypical and conventional antipsychotic prescriptions. The lower panel of the figure displays a graphical overview of the observed and expected numbers of pneumonia registrations in different time periods relative to the

antipsychotic prescription; the upper panel shows the corresponding relative rate with IC values.

Figure 1 shows the temporal pattern for 'pneumonia and other chest infections' recorded relative to atypical and conventional antipsychotic prescriptions for all ages. A sudden increase in the recording rate of pneumonia-related terms was noted after an antipsychotic prescription, compared with the period prior to prescription. Compared with patients with other prescriptions, a higher relative recording rate of the pneumonia-related terms was noted after antipsychotic prescriptions.

Figure 2 displays the chronographs for acute chest infections recorded before and after atypical and conventional antipsychotic prescriptions for patients aged  $\geq 65$  years. The corresponding result for patients aged 18–64 years is shown in Figure 3. For patients aged  $\geq 65$  years, there was an unexpectedly higher relative rate of terms within the acute chest infections group, recorded after atypical





antipsychotic prescriptions, compared with before. For the conventional antipsychotics, the difference of acute chest infections before and after prescription was much smaller.

The temporal pattern for bronchopneumonia in patients aged  $\geq 65$  years was similar for atypical and conventional antipsychotic prescriptions, with a relative increase of registrations in the month after prescription, continuing for several months (Figure 4). In the years preceding the antipsychotic prescription, there were few registrations of bronchopneumonia, resulting in a fluctuating relative rate, although for the conventional antipsychotics the relative rate had already been increasing before prescription took place.

The hypostatic pneumonia group, including aspiration pneumonitis, had few registrations of this category, particularly in the atypical antipsychotic group (Figure 5). The conventional antipsychotics had an elevated relative rate on day of prescription

that continued at a similar level during the months after prescription.

The temporal patterns between the antipsychotics and the pneumonia-related terms, as seen in the above analyses, remained also when limiting the data to patients aged  $\geq 80$  years.

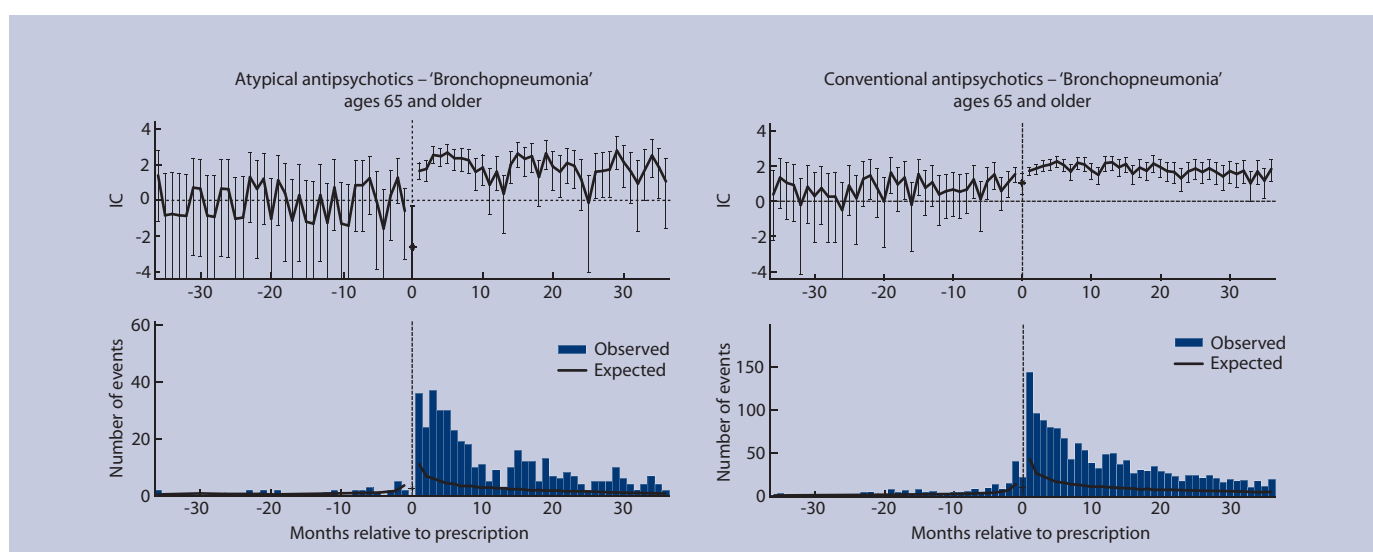
An increase of amoxicillin prescriptions was seen after atypical antipsychotic prescriptions, confirming the temporal pattern seen for acute chest infections subsequent to the same antipsychotic class (Figure 6). This was not seen for the conventional antipsychotics.

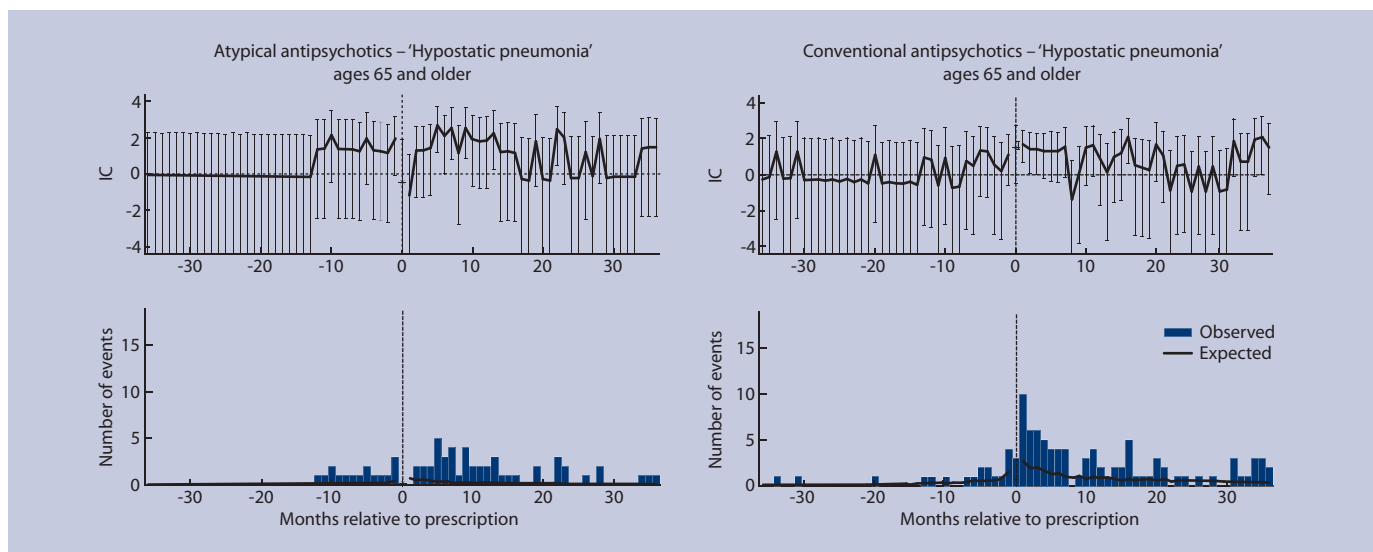
#### **Review of patients aged $\geq 65$ years with pneumonia-related terms recorded within the month after an antipsychotic prescription**

The account of details in this section regards the prescriptions for patients aged  $\geq 65$  years who had a pneumonia-related term recorded within the month after the antipsychotic prescription. The type and number of atypical and conventional antipsychotic

**Figure 3. Chronographs for records of acute chest infections relative to atypical and conventional antipsychotic prescriptions for ages 18–64 years. IC value on the day (month=0) for the IC graph was below -2 and outside the scale.**

**Figure 4. Chronographs for records of bronchopneumonia relative to atypical and conventional antipsychotic prescriptions for ages  $\geq 65$  years.**





**Figure 5. Chronographs for records of hypostatic pneumonia relative to atypical and conventional antipsychotic prescriptions for ages  $\geq 65$  years.**

prescriptions represented in each antipsychotic class for this group of patients is given in Table 1. The atypical and conventional antipsychotic prescriptions were, to a large extent, represented by risperidone and thioridazine respectively, which were also the top prescribed antipsychotics in the dataset.

The ICD-10 term that was mostly represented within the acute chest infections group in the month after prescription was 'unspecified acute lower respiratory infection' for both atypical and conventional antipsychotics (Table 2).

The median age for patients aged  $\geq 65$  years with registrations of acute chest infections terms in the month after atypical and conventional antipsychotic prescription was 85 and 83 years, respectively. The corresponding median age for bronchopneumonia was 83.5 years for atypical prescriptions and 84 years for conventional antipsychotic prescriptions.

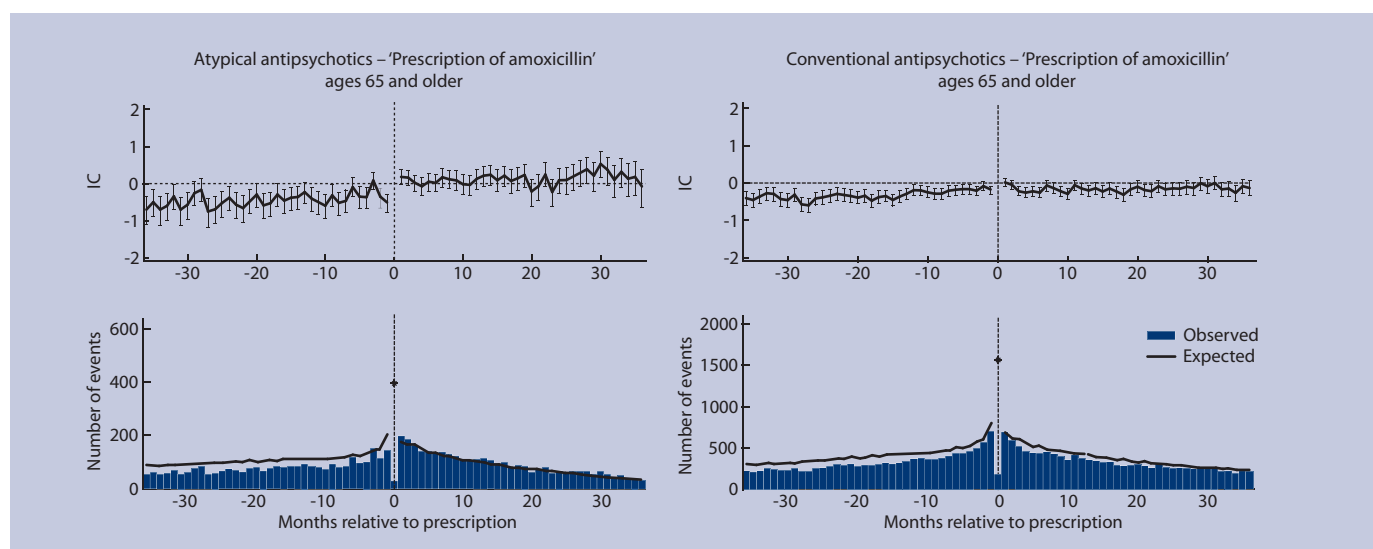
To increase understanding of the outcomes in the

patients ( $\geq 65$  years) who had acute chest infections and bronchopneumonia in the month after prescription, the rate of deregistrations in these patient histories were reviewed from time of antipsychotic prescription until the end of the month. A total of 86% of the patients with bronchopneumonia were deregistered within the month after an atypical antipsychotic prescription. The corresponding percentage for the patients with conventional antipsychotic prescriptions was 71%. The deregistration rate for patients with acute chest infections was 15% within the month after an atypical prescription and 20% after a conventional antipsychotic prescription. Death was the most common reason for deregistration.

## DISCUSSION

### Summary of main findings

In patients aged  $\geq 65$  years, an increased registration of acute chest infections subsequent to atypical



antipsychotic prescriptions was noted relative to the rate in the same patients prior to the prescription. An increased rate of acute chest infections was seen also relative to the background of older people having been prescribed other medications. The corresponding increase after conventional antipsychotic prescriptions was much smaller. Patients aged <65 years did not have a higher rate of chest infections after antipsychotic prescriptions, be they atypical or conventional.

Bronchopneumonia had a striking and persistent increase in the follow-up period after both atypical and conventional antipsychotic prescriptions. There was, however, an increase in the relative rate of bronchopneumonia before conventional antipsychotic prescriptions. Registrations of bronchopneumonia subsequent to antipsychotic prescriptions were also highly associated with records indicating death.

An elevated rate of registrations was noted for hypostatic pneumonia around the time of conventional antipsychotic prescriptions. This group of terms had few registrations, particularly for atypical prescriptions, making the evaluation more uncertain.

### Strengths and limitations of this study

The recorded diagnosis of pneumonia and related terms in this study of electronic health records is based on clinical evidence and not confirmed by radiological, or any other, tests. The study is dependent on the codes assigned by GPs and could be subject to misclassification bias. As for any study based on issued prescription records, it is not known if the patient actually took the medication prescribed. Observational data will commonly be unsatisfactory, to various degrees, because it is not collected for a specific research reason; on the other hand, it reflects the way normal clinical practice is done, rather than ideal interventions, which may not be generalisable.

Due to the dataset used in this study, the results do not represent all types of antipsychotic drugs. Some antipsychotics dominated more than others and some drugs, such as clozapine, had very few prescriptions. Thioridazine was noted to be a commonly prescribed conventional antipsychotic in this data; however, this drug has been withdrawn in many countries, including the UK, due to its adverse cardiac effects.<sup>12</sup> However, when this drug was excluded from the analysis it made no difference to the overall results. It is also important to consider the heterogeneity of the various drugs represented within the atypical and conventional antipsychotic classes in this study, as well as the limitations of using the current groupings of antipsychotic drugs as highlighted by Leucht *et al.*<sup>13</sup>

**Table 1. Number and type of atypical and conventional antipsychotic prescriptions with a pneumonia-related term recorded in the month after prescription, ages ≥65 years.**

	Acute chest infections	Bronchopneumonia	Hypostatic pneumonia
<b>Atypical antipsychotics</b>			
Risperidone	103	27	0
Olanzapine	25	9	0
Quetiapine	16	0	0
Amisulpride	2	0	0
Total atypical	146	36	0
<b>Conventional antipsychotics</b>			
Thioridazine	117	62	3
Haloperidol	77	37	3
Promazine	37	8	2
Chlorpromazine	30	17	1
Trifluoperazine	22	2	1
Flupentixol	17	3	0
Sulpiride	10	2	0
Levomopromazine	5	8	0
Zuclopenthixol	4	1	0
Droperidol	3	1	0
Perphenazine	2	1	0
Benperidol	2	0	0
Fluphenazine	0	1	0
Fluspirilene	0	1	0
Total conventional	326	144	10

**Table 2. ICD-10 terms for patients in the 'acute chest infections' group recorded in the month after antipsychotic prescription, ages ≥65 years.**

ICD-10 terms following antipsychotic prescriptions	Atypical prescriptions	Conventional prescriptions
Unspecified acute lower respiratory infection	125	281
Pneumonia, unspecified	15	31
Influenza with pneumonia, virus not identified	3	2
Viral pneumonia, unspecified	1	3
Pneumonia due to <i>Streptococcus pneumoniae</i>	1	5
Other bacterial pneumonia	1	1
Lobar pneumonia, unspecified	–	2
Bacterial pneumonia, unspecified	–	1

ICD = International Classification of Diseases.

The most commonly recorded ICD-10 term within 'acute chest infections' concerned 'unspecified acute lower respiratory infection', which is a commonly used term overall; this dominated the other terms included in the group.

The duration of the antipsychotic prescriptions has not been considered in the graphical display of pneumonia-related medical-event registrations; hence, in cases of late onset, the patient may not have been a current user of the medicine when the event occurred.

Records of fatal outcome obviously cannot precede prescription. As such, cautious interpretation is needed when comparing the 'before' and 'after' prescription pattern of medical events

most commonly associated with fatal outcome, as shown for bronchopneumonia.

A case-by-case evaluation to determine the possible causal relationship between the drug and the recorded event for individual patients has not been done in this study, and co-recorded events or prescriptions have not been evaluated. Instead, this analysis offers a way to highlight overall patterns of records before and after prescription, accounting for biases like expected clusters of events around prescriptions in general.

Without further analysis, it is not possible to identify any causative mechanism or factor leading to chest infections among older people who have been prescribed an antipsychotic drug. However, this study shows the temporal recording pattern of pneumonia and other acute chest infections in outpatients, not only after prescription but also before, sharpening the picture of the course of events in these patients.

#### Comparison with existing literature

The higher rate of chest infections after prescription of atypical antipsychotics is in line with Knol *et al*'s study,<sup>7</sup> where a stronger association between atypical antipsychotics and pneumonia was also seen, as compared with conventional antipsychotics. Users of conventional antipsychotics had a higher risk of death from infections, including pneumonia, than users of atypical antipsychotics in Setoguchi *et al*'s study,<sup>4</sup> but the difference was not statistically significant. A comparison with this study is complicated, given that different conventional antipsychotics are dominant in Setoguchi *et al*'s study, and because they investigated mortality while the current study examined pneumonia-related terms, irrespective of outcome. Loxapine was the most commonly prescribed conventional antipsychotic in Setoguchi *et al*'s study,<sup>4</sup> whereas thioridazine was the most commonly prescribed conventional antipsychotic in the current dataset, with loxapine being a rarely prescribed drug.

Drug effects, possibly leading to pneumonia after antipsychotic prescriptions, in older people were reviewed by Knol *et al*.<sup>7</sup> They mention xerostomia, dysphagia, dyskinesia, and sedation, which could result in swallowing problems, thereby causing aspiration pneumonia. In the current study there were few registrations specifically stating diagnoses suggestive of aspiration. However, it is plausible that GPs used a more general pneumonia term to record consequences of aspiration. Granulocytopenia is another disorder possibly caused by antipsychotics that could lead to a greater susceptibility of infection, resulting in the development of pneumonia. However, the increases in rates of serious acute chest

infections soon after first use of an antipsychotic seen in this analysis are unlikely to be due to granulocytopenia, as (after first exposure) it takes some time to develop, and the infection occurs at an even later date.

The occurrence of acute chest infections after the prescription of antipsychotics in the present study could also be explained by other events and need not be a direct effect of the antipsychotic medicine. Pneumonia in older people may present with sudden psychiatric disturbances, such as confusion, agitation, or psychosis, while fever may not be prominent.<sup>14</sup> In such patients, antipsychotics may be prescribed when the infection is not recognised,<sup>7</sup> or to help manage the patient if it is. Likewise, in such patients, both the use of antipsychotics and serious illness and death would be more likely to occur. Confounding possibilities also exist for psychiatric disorders and pneumonia in older people in primary care situations, such as neoplasia with cerebral secondaries, self neglect, alcoholism, and more.

Bronchopneumonia was commonly recorded in connection to fatal outcome in this study, and death often occurred in the first weeks of antipsychotic use among the subset of older people studied more in detail. A Swedish study on autopsy reports revealed that far more patients with a terminal illness and dementia died from bronchopneumonia (38.4%) than older people in general (2.8%).<sup>15</sup> This might explain why bronchopneumonia is recorded in temporal association with antipsychotic prescriptions given for patients with dementia, and could be seen as a natural course of their disease. However, it is interesting that the recording of bronchopneumonia commences so soon after first prescriptions of antipsychotic medicines, as seen in this study.

#### Implications for future research

As this study on outpatient records with chest infections following atypical antipsychotic prescriptions in older people confirms Knol *et al*'s study on hospitalised patients,<sup>7</sup> a causal relationship seems suggestive. Such an association would be of particular importance to patients with bronchopneumonia, as this diagnosis seems highly connected to fatal outcome. In the absence of a mechanism, further investigation of the role of antipsychotics in older people is needed.

#### Funding body

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#### Competing interests

Kristina Star has stocks in AstraZeneca. All other authors declare they have no competing interest relevant to this study.

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## Discuss this article

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## REFERENCES

1. US Food and Drug Administration. *Public health advisory: deaths with antipsychotics in elderly patients with behavioural disturbances*. Silver Spring: US Food and Drug Administration, 2005. <http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm053171.htm> (accessed 15 Apr 2010).
2. US Food and Drug Administration. *Information for healthcare professionals: conventional antipsychotics*. Silver Spring: US Food and Drug Administration, 2008. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm> (accessed 15 Apr 2010).
3. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005; **294**: 1934–1943.
4. Setoguchi S, Wang PS, Alan Brookhart M, *et al.* Potential causes of higher mortality in elderly users of conventional and atypical antipsychotic medications. *J Am Geriatr Soc* 2008; **56**: 1644–1650.
5. Barnett MJ, Perry PJ, Alexander B, Kaboli PJ. Risk of mortality associated with antipsychotic and other neuropsychiatric drugs in pneumonia patients. *J Clin Psychopharmacol* 2006; **26**: 182–187.
6. Wada H, Nakajoh K, Satoh-Nakagawa T, *et al.* Risk factors of aspiration pneumonia in Alzheimer's disease patients. *Gerontology* 2001; **47**: 271–276.
7. Knol W, Van Marum RJ, Jansen PA, *et al.* Antipsychotic drug use and risk of pneumonia in elderly people. *J Am Geriatr Soc* 2008; **56**: 661–666.
8. Electronic Medicine Compendium. *Summary of product characteristics*. Leatherhead: Datapharm Communications Ltd, 2009. <http://www.medicines.org.uk/> (accessed 15 Apr 2010).
9. De Lusignan S, Stephens P, Adal N, Majeed A. Does feedback improve the quality of computerized medical records in primary care? *J Am Med Inform Assoc* 2002; **9**: 395–401.
10. Norén GN, Hopstadius J, Bate A, *et al.* Temporal pattern discovery in longitudinal electronic patient records. *Data Mining and Knowledge Discovery* 2010; **20**: 361–387.
11. European Pharmaceutical Market Research Association. *Anatomical classification*. <http://www.ephmra.org/classification/anatomical-classification.aspx> (accessed 14 Apr 2010).
12. Sweetman S, ed. *Martindale: the complete drug reference*. London: Pharmaceutical Press, 2010.
13. Leucht S, Corves C, Arbter D, *et al.* Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009; **373**: 31–41.
14. Venkatesan P, Gladman J, Macfarlane JT, *et al.* A hospital study of community acquired pneumonia in the elderly. *Thorax* 1990; **45**: 254–258.
15. Brunnström HR, Englund EM. Cause of death in patients with dementia disorders. *Eur J Neurol* 2009; **16**: 488–492.

Appendix 1. ICD terms and Read Codes<sup>a</sup> for 'acute chest infections'.

ICD-10 code	ICD-10 term	Read Code	Read term
J110	Influenza with pneumonia. Virus not identified	.H3.. .H351 .H3Z. H270. H2700 H270z H2y.. H200. H201. H20y. .H31. H20.. H20z.	Pneumonia and influenza Influenza + pneumonia Pneumonia/influenza NOS Influenza + pneumonia Influenza + bronchopneumonia Influenza + pneumonia NOS Pneumonia or influenza OS Pneumonia — adenovirus Pneumonia — resp.syncyt.virus Pneumonia — virus NEC Viral pneumonia Viral pneumonia Viral pneumonia NOS
J120	Adenoviral pneumonia		
J121	Respiratory syncytial virus pneumonia		
J128	Other viral pneumonia		
J129	Viral pneumonia, unspecified		
J130	Pneumonia due to streptococcus pneumoniae	.H32. H21.. H222. H220. H221. H224. H223. H22yX	Lobar-pneumococcal — pneumonia Lobar (pneumococcal) pneumonia Pneumonia — H.influenzae Pneumonia — klebsiella pneum. Pneumonia — pseudomonas Pneumonia — staphylococcal Pneumonia — streptococcal Pneumonia — aerobic grm-ve bact
J140	Pneumonia due to haemophilus influenzae		
J150	Pneumonia due to klebsiella pneumoniae		
J151	Pneumonia due to pseudomonas		
J152	Pneumonia due to staphylococcus		
J154	Pneumonia due to other streptococci		
J156	Pneumonia due to other aerobic Gram-negative bacteria		
J157	Pneumonia due to mycoplasma pneumoniae	.H342 H231.  H232. H28.. H22.. H22y. .H341 H22yz H22z. H233. H23.. H23z. H260. H2600 H261. H20y0	Mycoplasma pneumonia Pneumonia — mycoplasma pneumon Pneumonia — PPLO Atypical pneumonia Other bacterial pneumonia Pneumonia — other specif.bact. Bacterial pneumonia NOS Pneumonia — bacteria NOS Bacterial pneumonia NOS Chlamydial pneumonia Pneumonia — specif.organisms Pneumonia—spec.organism NOS Lobar pneumon-unspec organism Lung consolidation Basal pneumon-unspec organism [X]Oth pneumonia,organsm unspf
J158	Other bacterial pneumonia		
J159	Bacterial pneumonia, unspecified		
J160	Chlamydial pneumonia		
J168	Pneumonia due to other specified infectious organisms		
J181	Lobar pneumonia, unspecified	H20y0 .H34. .H34Z H2.. H24.. H26.. H262. H2z.. .H346	Severe acute respiratory syndr Pneumonia NOS Pneumonia NOS Pneumonia and influenza Pneumonia + Infect.disease EC Pneumonia, organism unspecif. Postoperative pneumonia Pneumonia or influenza NOS Bilateral pneumonia
J188	Other pneumonia, organism unspecified	.H1.. .H163 .H1Z. .H6ZA .H6ZB H0.. H062. H06z0 H06z1 H06z2 H0y.. H0z.. SP132	Acute respiratory infections Acute low respitract infection Acute resp. infection NOS Chest infection NOS Lower respiratory tract infect Acute respiratory infections Acute low respitract infection Chest infection NOS Lower resp tract infection Recurrent chest infection Acute respiratory infectns.OS Acute respiratory infectn.NOS Post operative chest infection
J189	Pneumonia, unspecified		
J220	Unspecified acute lower respiratory tract infection		

<sup>a</sup>GP 4-byte set and 5-byte set Read Codes. ICD = International Classification of Diseases.

**Appendix 2. ICD terms and Read Codes<sup>a</sup> for bronchopneumonia.**

ICD-10		Read	
code	ICD-10 term	Code	Read term
J180	Bronchopneumonia, unspecified	.H33.	Bronchopneumonia
		H25..	Bronchopneumonia,organism unsp

<sup>a</sup>GP 4-byte set and 5-byte set Read Codes. ICD = International Classification of Diseases.

**Appendix 3. ICD terms and Read Codes<sup>a</sup> for 'hypostatic pneumonia'.**

ICD-10		Read	
code	ICD-10 term	Code	Read term
J182	Hypostatic pneumonia, unspecified	.H6Z4	Hypostatic bronchopneumonia
		H5400	Hypostatic pneumonia
		H5401	Hypostatic bronchopneumonia
J690	Pneumonitis due to food and vomit	.H53.	Aspiration pneumonia
		H470.	Pneumonitis-food/vomit inhal.
		H4703	Pneumonitis-vomit inhalation
		SP131	Other asp.pneumonia after care
J691	Pneumonitis due to oils and essences	H471.	Pneumonitis-oil/essence inhal.
		H4710	Lipoid pneumonia (exogenous)
J698	Pneumonitis due to other solids and liquids	H47..	Pneumonitis - solids/liquids
		H47y.	Pneumonitis-other solid/liquid
		H47yz	Pneumonitis-solid/liquid NOS
		H47z.	Pneumonitis-solid/liquid NOS

<sup>a</sup>GP 4-byte set and 5-byte set Read Codes. ICD = International Classification of Diseases.