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Drugs that increase the risk of community-acquired pneumonia: a narrative review

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Abstract

Introduction: Community-acquired pneumonia (CAP), a major cause of morbidity and mortality, is the leading infectious cause of death in the developed world. Population-based studies and systematic reviews have identified a large number of risk factors for the development of pneumonia in adults. In addition to age, lifestyle habits, and comorbidities, some forms of pharmacotherapy may also increase the risk for CAP.

Areas covered: MEDLINE, CENTRAL, and Web of Science were used in 2017 to search for case-control, cohort studies, as well as randomized controlled trials and meta-analysis that involved outpatient proton pump inhibitors (PPIs), inhaled corticosteroids (ICSs), antipsychotics, oral antidiabetics, and CAP diagnosis in patients aged > 18 years.

Expert opinion: Our review confirmed that the use of ICSs, PPIs or antipsychotic drugs was independently associated with an increased risk for CAP. We also identified a positive association between specific oral antidiabetics and the development of pneumonia.

Keywords: community-acquired pneumonia, risk factors, antipsychotics, inhaled corticosteroids, proton pump inhibitors

Article highlights

1. Several studies and randomized controlled trials reveal that some forms of pharmacotherapy, such as inhaled corticosteroids, proton pump inhibitors, and antipsychotic drugs, may increase the risk for CAP.
2. Data from RCTs and observational studies show increased rates of pneumonia in COPD patients treated with ICS, especially in those receiving higher doses, although this risk is not associated with higher mortality.
3. Proton pump inhibitors increase the risk for CAP, with the risk being highest at the beginning of therapy.
4. There is an association between antipsychotic drug use in elderly patients and pneumonia. The risk for pneumonia varies for the different classes of antipsychotics, being higher for atypical antipsychotics.
5. There is an obvious need for prospective trials to define the dose-dependent risk for pneumonia associated with each of these types of drugs and whether there are differences between different populations of patients.

1. Introduction

Pneumonia frequently results in hospital admission and is a risk factor for prolonged hospital stays, placing a considerable financial burden on healthcare services (1). Reported annual incidences, which range from 1.6 to 16 cases per 1,000, vary between countries, probably due to differences in diagnostics, reporting, and socioeconomic factors (2). Prevalence and mortality are higher in elderly patients and will therefore further increase in the aging population of developed countries. The mortality rate varies between 0.1 and 0.7 cases per 1,000 each year. Community-acquired pneumonia (CAP) also has long-term implications for subsequent mortality. In a study from the Netherlands, the 1-, 5-, and 7-year mortality rates in patients who had recovered from CAP were reported to be significantly higher at 17%, 43%, and 53%, respectively, than those in age- and sex-matched population controls (4%, 19%, and 24%, respectively) (3). Targeted interventions to reduce the risk of developing CAP, based on understanding and recognizing the risk factors for CAP, are of primary importance in decreasing CAP-related mortality (4).

Studies from high-income countries have identified several risk factors for CAP including age, smoking (5, 6), earlier cases of pneumonia, environmental exposure to different substances, immunosuppression, comorbidities such as asthma and chronic obstructive pulmonary disease (COPD) (7,8), as well as recent viral upper respiratory tract infections (URTI) (9). In addition, low body mass index (BMI), contact with children, and poor dental hygiene have also been identified as risk factors for CAP in a systematic literature review and meta-analysis of studies undertaken in Europe (5). Recently, it has been shown that medications administered to patients for underlying diseases (e.g., COPD, asthma, cardiac failure, ulcer, hypertension, dementia, and Alzheimer's disease) may also influence the development of pneumonia and its course (4, 10, 11,12,13). Collectively, the current literature is inconclusive; the majority of randomized clinical trials (RCTs) were not designed with pneumonia as a prespecified or adjudicated endpoint, observational studies were not population-based and had a relatively short follow-up time and different statistical methods. Therefore, they not always report conclusive and concordant results.

Because of this heterogeneity, there is a need to update all the evidence to reach a more definitive conclusion for the studied drugs. We will critically review the evidence from RCTs, observational studies, reviews and meta-analyses linking pharmacotherapeutic agents and risk of pneumonia.

2. Methods

A search was conducted in Medline to identify studies exploring the association between risk of pneumonia and medication use. All studies had to be in English language and had to concern drug use as an intervention in persons >18 years old and for any indication, provided that the outcome was pneumonia.

The PubMed database was searched using the following search string: pneumonia AND English AND 2005/01/01–2017/11/31 AND risk OR clinical trial, phase III OR controlled clinical trial OR observational study OR RCT or case reports or practice guideline or editorial or review. References of relevant original research as well as review articles were hand-searched to identify further studies.

Two investigators (A. L. and A. T.) independently examined all titles and abstracts and obtained full texts of potentially relevant papers. The included articles were reviewed in full and data on the study setting and methodology, characteristics of the populations studied, risk estimate, pathogens and antibiotic treatments were extracted.

3. Risk of developing CAP by drug type

The most studied drugs that increase the risk of pneumonia are the inhaled corticosteroids (ICSs), the Proton pump inhibitors (PPIs), the oral antipsychotics and antidiabetics agents. There are references about the potential role of diuretics, digoxin, N-acetylcysteine, any vitamin intake and oral anticholinergic agents (11,13) in the development of pneumonia. But the effect of the abovementioned drugs as potential risk factors for CAP should be confirmed in further studies.

3.1. Inhaled corticosteroids (ICSs)

To prevent and treat COPD, combinations of ICS and long-acting β_2 agonists (ICS/LABA) are recommended based on evidence from studies such as TORCH and INSPIRE (14, 15). However, recent results from the FLAME study have raised doubts about this strategy (16). In patients with COPD, RCTs (17- 22), meta-analyses (23-27), and observational studies (28-34) have generally observed an increased risk for pneumonia associated with the use of ICS-containing medication (Table 1).

Randomized controlled trials (RCTs)

The impact of ICS on pneumonia was unexpectedly documented in the TORCH study, which was designed to assess the benefits of inhaled drugs on long-term survival in COPD patients (14). The TORCH study revealed an increased risk for pneumonia in COPD patients treated with fluticasone (FC) (HR, 1.52; 95% confidence interval (CI): 1.32-1.76) alone and in combination with salmeterol (SAL). The incidence of pneumonia increased significantly in patients treated with FC alone (18.3%) or in combination with SAL (19.6%) compared to patients treated with placebo (12.3%) (35).

Similarly, Crim et al. (20), in a post-hoc analysis of TORCH study, analysed and identified potential risk factors for adverse event reports of pneumonia noted an approximately 50% increase in the risk for pneumonia (HR, 1.52; 95% CI: 1.32-1.76) among those treated with fluticasone propionate (FP) compared to those on placebo.

In a 12-month RCT involving 1,219 patients with severe FEV1 of < 50%, Sharafkhaneh et al. proved that BUD presented a dose-related risk for pneumonia (22). The incidence of pneumonia was higher in the BUD/F pMDI groups than in the F group, as well as in the 320/9 mg BUD/F pMDI group than in the 160/9 mg BUD/F pMDI group (6.4% vs. 4.7% vs. 2.7%, respectively).

In a cohort of 163,514 patients (21), of whom 20,344 had a serious case of pneumonia during the 5.4 years of follow-up (incidence rate 2.4/100/year), current use of ICS was associated with a 69% increase in the incidence of serious pneumonia (RR, 1.69; 95% CI: 1.63-1.75). The risk continued with long-term use and declined gradually after stopping ICS treatment, disappearing after 6 months (RR, 1.08; 95% CI: 0.99-1.17). The incidence of serious pneumonia was higher for FC (RR, 2.01; 95% CI: 1.93-2.10), increasing with the daily dose, but much lower for budesonide (BUD) (RR, 1.17; 95% CI: 1.09-1.26).

Similarly, one year ago, a secondary analysis of the large UPLIFT study revealed that the incidences of pneumonia were significantly higher in patients taking ICS than in those not on ICS (0.068 vs. 0.056, respectively; $p = 0.012$), with the patients on FC showing a higher rate of pneumonia than those on other types of ICSs (0.077 vs. 0.058, respectively; $p < 0.001$) (31).

However, as a previous study of Mapel et al (33), a very recently published RCT did not observe an increased risk for pneumonia with ICS treatment (vilanterol 25 μg (VI), fluticasone furoate 100 μg (FF), vilanterol 25 μg combined with 100 μg fluticasone furoate (FF/VI), or matched placebo) in COPD subjects with moderate airflow limitation and heightened cardiovascular risk (34).

Likewise, Festic et al. (36) performed a secondary analysis of an established database ($n=5584$) from a lung injury study (LIPS), to evaluate the possibility that prehospital ICS use predisposes COPD patients to pneumonia. After adjusting for multiple confounders, the adj OR for participants with COPD was 1.40 (95% CI, 0.95-2.09) and was not statistically significant ($p=0.93$).

Observational studies

The association between ICS use and pneumonia has also been examined in population-based cohort studies of COPD. Starting, a case-control epidemiological study in Canada (28) published in 2007, compared the rates of ICS use in elderly COPD patients who were hospitalized due to pneumonia with those in 95,768 controls. ICS use was associated with a dose-dependent increased risk for hospitalization due to pneumonia (RR, 1.70; 95% CI: 1.63–1.77) and increased pneumonia-related mortality at 30 days (RR, 1.53; 95% CI: 1.30–1.80). The rate ratio of hospitalization due to

pneumonia was the highest with the largest doses of ICS used, which was equivalent to 1,000 µg/day or more of FC (RR, 2.25; 95% CI: 2.07-2.44).

Müllerova et al. (7) examined the risk of CAP in a cohort of 40,411 COPD patients. The authors showed that patients with COPD who were treated with an ICS were more likely to develop CAP. In an observational cohort study from the UK, ICS-containing medication administered to new users was associated with an increased risk for hospitalization due to pneumonia (HR, 1.55; 95% CI: 1.14-2.10) and for pneumonia (HR, 1.49; 95% CI: 1.22-1.83). The increased risk for pneumonia decreased for treatments with ICS lasting > 1 month or > 6 months in the new users. There was also an apparent dose-related effect, with higher daily doses of ICSs (32).

The varying levels of risk associated with the different types of ICSs was also apparent in the PATHOS study (29), which revealed that the rates of pneumonia and hospital admissions were higher in patients treated with FC/SAL (rate ratios of 1.73 (95% CI: 1.57-1.90; $p < 0.001$) and 1.74 (95% CI: 1.56-1.94; $p < 0.001$), respectively) than in those on BUD/formoterol (F). However, the study had some limitations as the majority of the fixed-dose treatments prescribed were BUD/F (72%) and the authors compared a high daily dose of FC (783 ± 338 mcg/day) to a medium daily dose of BUD (568 ± 235 mcg/day), without analyzing equipotent doses and similar time periods.

Meta-analyses

Several meta-analyses have evaluated the association of ICS use in patients with COPD and the risk of developing pneumonia (23,24,25,27).

Drummond et al. (23) identified 11 RCTs of stable COPD patients treated with ICSs. The authors conclude that administration of ICSs is associated with a 34% increased risk of developing pneumonia, colleagues found a dose- and time-related effect. In a Cochrane meta-analysis that included 43 studies, 26 on FC (n = 21,247) and 17 on BUD (n = 10,150), FC was associated with a higher risk for any type of pneumonia (i.e., less serious cases treated in the community) than BUD (OR, 1.86; 95% CI: 1.04-3.34) (25).

Festic et colleagues (27), two years ago, performed a meta-analysis of 38 studies: 29 RCTs and 9 observational studies. The estimated unadjusted risk of pneumonia was increased in RCTs: RR 1.61; 95% CI 1.35-1.93, $p < 0.001$; as well as in observational studies: OR 1.89; 95% CI 1.39-2.58, $p < 0.001$.

On the contrary, a meta-analysis performed by Sin et al. showed that BUD did not increase the risk for pneumonia in patients with COPD (26).

3.2. Proton pump inhibitors (PPIs)

Proton pump inhibitors (PPIs) are among the most widely prescribed medications and are used to provide long-lasting reduction in gastric acid production. They are widely used to prevent the development of ulcers and treat gastrointestinal diseases, such as dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, Barrett's esophagus, and stress-induced gastritis. In 2011, omeprazole was the sixth most commonly prescribed drug in the United States with nearly 60 million prescriptions (37). Additionally, it has been reported that in approximately 40% of older adult long-term PPI users, there is no indication for PPI use (38).

Observational studies and a few RCTs in the last decade have yielded inconsistent findings about the association between PPI use and the risk for pneumonia. This side effect of PPIs is clearly time dependent as indicated by the studies mentioned below (Table 2).

RCTs

Sugano et al (39) in a RCT involving 99 sites in Japan for 1 year, was designed to compare the efficacy of lansoprazole (15 mg daily) with gefarnate (50 mg twice daily) in patients with a history of gastric or duodenal ulcers who required long-term NSAID therapy. In the case of pneumonia, a causal relationship with the study medication was denied in all patients in this study.

Observational studies

A large population study from the Netherlands (40) analyzed a cohort of occasional users of PPIs and found the incidence of pneumonia to be 2.45 per 100 individuals per year.

Gulmez et al. in 2007 reported an increased risk for CAP in the general population (OR, 1.5; 95% CI: 1.3-1.7) among PPI users, but not among those taking H₂-receptor antagonists (H₂RA) (adjusted OR, 1.10; 95% CI: 0.8-1.3) (41). The authors stated that the recent initiation of PPI treatment (0-7 days prior to a CAP episode) resulted in a strong association with the risk for CAP (OR, 5.0; 95% CI: 2.1-11.7). However, neither a dose-response relationship nor a cumulative effect was

found. Similarly, Myles et al. (42) reported that current PPI prescriptions were associated with a significantly increased risk for pneumonia of nearly 55% in a large population-based case-control study of 3,709 pneumonia cases and 22,174 controls (adjusted OR, 1.55; 95% CI: 1.38-1.77).

Accordingly, a large population-based case-control study using primary care data from the UK reported that newly-diagnosed CAP cases increased with the current use of PPIs (RR, 1.16; 95% CI: 1.03–1.31), but not H₂RA (RR, 0.98; 95% CI: 0.80 –1.20). However, an increased risk for pneumonia was evident only in the first 12 months of PPI treatment, with some evidence of a dose response (43). Sarkar et al. (44) reported that, overall, current PPI use was not associated with an increased risk for pneumonia (OR, 1.02; 95% CI: 0.97–1.08); this association only occurred when PPI therapy had been started in the previous 30 days (OR, 1.96; 95% CI: 1.69–2.29). Additionally, there were no associations between CAP and H₂RA treatment and between CAP and PPI administered to adults > 60 years old.

A recently published large population-based study from Taiwan, which included 1,572 dementia patients, identified PPI use to be an independent risk factor for pneumonia (45). Interestingly, PPIs were found to double the risk for CAP in a dose-dependent manner.

PPI-associated increases in susceptibility to respiratory infections are likely to be due to the PPI-mediated increases in gastric pH, which promotes bacterial colonization and transfer to the respiratory system. However, in contrast to PPIs, H₂RAs have not been associated with an increased risk for pneumonia (41,42,43). This difference might reflect the higher potency of PPIs compared to H₂RAs. Moreover, Walentek et al. (46) indicated that PPI-associated pneumonia in human patients might, at least in part, be linked to the dysfunction of the mucociliary epithelia of the airways.

However, a case-control study performed in the US in older adults concluded that the current use of PPI and H₂RA was not associated with an increased risk for CAP (adjusted OR, 1.03; 95% CI: 0.86–1.24) in a fully adjusted analysis (47). When the association between CAP and PPI use by indication was analyzed, the authors of the study observed a greater increase in risk among patients taking these medications for peptic ulcers or dyspepsia than among those taking the drugs for gastroprotection or gastroesophageal reflux disease.

Meta-analysis

Johnston et al (48) in a meta-analysis of 6 nested case-control studies, found an increased risk of CAP associated with PPI use [OR 1.36 (95% CI 1.12–1.65)]; significant heterogeneity remained (I² 92%, P < 0.001). Eom and colleagues (49) conducted a meta-analysis of eight observational studies and found that PPI use was associated with a 27% increased risk for either hospital-acquired pneumonia (HAP) or CAP (adjusted OR, 1.27; 95% CI: 1.11-1.46). An increased risk for CAP with PPI use was also observed when only five of the studies were analyzed (adjusted OR, 1.34; 95% CI: 1.14-1.57). Importantly, there was a strong temporal effect, with treatments of < 7 days being associated with a three-fold increase in the risk for pneumonia (adjusted OR, 3.95; 95% CI: 2.86-5.45). Several years later, Lambert et al. (50) analyzed 26 studies involving a total of 226,769 CAP cases among 6,351,656 participants. They observed a pooled risk for CAP with ambulatory PPI therapy of 1.49 (95% CI: 1.16-1.92), which increased during the first month of treatment (OR, 2.10; 95% CI: 1.39-3.16), regardless of PPI dose or the age of the patient. Of note, this meta-analysis did not find an association between the risk for CAP and H₂RA treatment (OR, 1.00; 95% CI: 0.90–1.12).

On the contrary, Filion et al (51) formed eight restricted cohorts of new users of NSAIDs, and after meta-analysis, support that PPIs are not associated with an increased risk of hospitalization for CAP (adjOR=1.05; 95% CI 0.89 to 1.25).

3.3. Antipsychotic agents

Antipsychotic drugs (APs) are generally categorized as typical antipsychotic drugs (TAPs), such as butyrophenones (e.g., haloperidol) and phenothiazines (e.g., thioridazine), or the newer class of atypical antipsychotic drugs (AAPs), such as clozapine, risperidone, olanzapine, and quetiapine. Antipsychotics are primarily indicated in the treatment of schizophrenia and the manic phases of bipolar disorder. However, these drugs are also frequently used off-label. In recent years, antipsychotics have been increasing used worldwide to treat the behavioral and psychological symptoms of dementia (BPSD). According to the 2004 National Nursing Home Survey, one in four elderly nursing home residents in the USA had received APs, with 94.5% receiving AAPs (52).

In June 2008, the FDA warned about the increased risk for all-cause mortality in elderly patients with dementia treated with TAPs (53), the usual causes of death being heart-related events and infections (primarily pneumonia). In Europe, the UK Department of Health commissioned the National Dementia and AP Prescribing (DAP) audit, which suggested a reduction in AP prescribing by half between 2008 and 2011 (54, 55). With the safety warnings there was a sustained 25 % reduction in AP use between 2010 and 2012 in the UK (from a quarterly prevalence of 14 to 11 %), whereas a

substantial increase in total AP use (to 32 % in 2012) was observed in Italy.

Data from several studies, mainly in elderly patients, suggest that the use of APs is associated with a moderate increase in the risk for CAP (56-59). Trifiró et al (57) used a nationwide general practice database to investigate fatal and non-fatal pneumonia and discovered that the use of either AAPs or TAPs in elderly patients was associated with an increased risk for CAP in a dose-dependent manner. No clear pattern between the risk for CAP and treatment duration has been found to date, although two studies have observed the risk to be highest during the early phase of treatment with APs (10, 57). Moreover, Knol et al. (58) observed a 60% increased risk for pneumonia during the first week of treatment with 'anti-psychotic' medication, the greatest increase in risk being found for the AAPs. By contrast, Aparasu et al. (59) found no differences in the risk for pneumonia between TAPs and AAPs in a retrospective cohort of 49,904 new users of APs among eligible nursing home residents.

Gambassi et al. (60), estimating the risk-benefit ratio for prescribing APs, suggested that there was 1 hospitalization for pneumonia for every 2-5 patients showing any clinical improvement in symptoms in response to treatment with APs. In a nested case-control study that followed patients aged 18-65 years with schizophrenia over eight years, Kuo et al. (61) found that the use of second-generation antipsychotic drugs was associated with a 69% greater risk (adjusted RR = 1.69) of developing pneumonia, after taking into account confounding factors, with the magnitude of the association being the highest for clozapine. Although quetiapine, olanzapine, zotepine, and risperidone were also associated with an increased risk, there was no clear dose-dependent association. Wang et al. (62) reported that the risk for pneumonia was the highest within the first 30 days of treatment with APs (HR, 1.1; 95% CI: 0.76-1.38), decreasing after 60 days (HR, 1.03; 95% CI: 0.76-1.38) and disappearing after 120 days of treatment (HR, 0.84; 95% CI: 0.66-1.05). Likewise, Trifiró and colleagues (57) demonstrated that the risk for CAP lasted only in the first week of treatment (OR, 4.62; 95% CI: 2.05-10.38), decreasing thereafter. Similarly, Pratt et al. (63) observed a reduced risk with continuous treatment in a self-controlled case series, but only for AAPs.

Different levels of risk have been reported for the different types of antipsychotic drugs (57, 64), with risperidone shown to be associated with the highest risk for pneumonia (OR, 3.51; 95% CI: 1.94-6.36). Furthermore, a large population-based study assessing 92,234 new users of AAPs suggested that risperidone (HR, 1.14; 95% CI: 1.10-1.18) and olanzapine (HR, 1.10; 95% CI: 1.04-1.16) increased the risk for pneumonia in elderly patients compared to quetiapine (65).

Although it is highly possible that the sedative and anticholinergic side effects of the APs could increase the risk of aspirations by decreasing peristalsis, the exact mechanisms by which APs increase the risk for CAP are unclear and remain speculative (10). There is minimal risk for akinesia with AAPs, particularly when these drugs are used at low doses (66).

3.4. Oral antidiabetic agents

There are increased incidences of pneumonia, associated complications, and mortality among patients with diabetes (67). Like glucocorticoids in COPD, the immunomodulatory and glucocorticoid-like properties of antidiabetic drugs such as thiazolidinediones could increase susceptibility to lung infections.

There are a number of different types of antidiabetic drugs belonging to different classes as: biguanides (metformin), sulfonylureas (glipizide, glyburide, tolbutamide), thiazolidinediones (pioglitazone) and GLP-1 receptors agonists (exenatide, liraglutide). Dipeptidyl-peptidase-4 inhibitors (DPP4Is) (sitagliptin, saxagliptin, vildagliptin, linagliptin and alogliptin) are a new class of drugs for the treatment of type 2 diabetes mellitus (T2DM). Some drugs are combinations of some of these drug types.

Observational studies

A study that used data from the World Health Organisation's Adverse Drug Reactions database found a 12-fold increased risk of URTI among DPP4I users versus users of biguanides (68). (Table 4)

In a population-based cohort study (69) using data from the world's largest primary care database, the UK Clinical Practice Research Datalink (CPRD), including 211,049 NIAD users, current users of NIADs had a 1.6-fold increased risk of pneumonia, as compared with nondiabetic controls (adj. HR 1.56 ; [CI] 1.42-1.71). The risk of pneumonia was not increased with current DPP4I use versus use of other NIADs, [(HR) 0.70; 95% (CI) 0.55-0.91]. There was no further significant dose-effect relationship between pneumonia and DPP4I use. Accordingly, an observational study carried out in the UK found no association between the use of DPP-4 inhibitors and the risk of hospitalization from CAP [adj(OR) 0.80; (0.50-1.29)] (70).

However, there are differences in the level of risk for pneumonia among drugs from the same category. A recent cohort study using a Danish nationwide population database (71) involving 131,949 patients with T2DM showed that those who had started treatment with sulfonylureas had a slightly or a substantially higher risk for hospitalization caused by pneumonia than those who had initiated treatment with metformin (HR, 1.12; 95% CI: 1.08-1.16) or insulin (HR, 1.63; 95% CI: 1.54-1.72), respectively.

Gorricho et al. (72) in a case-control study reported that the use of any combination involving thiazolidinediones was associated with a higher risk for CAP (adjusted OR, 2.00; 95% CI: 1.22-3.28), which was double the risk associated with metformin plus sulfonylurea treatment.

Review and Meta-analysis

The higher rate of chest infections among diabetic patients after being prescribed antidiabetics is in line with a Cochrane review of short-term clinical trials (< 6 months) (73) that demonstrated a strong association between orally active DPP-4 inhibitors, like sitagliptin, and pneumonia. Vildagliptin was also associated with an increased incidence of infections, but this did not reach statistical significance.

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Singh et al. (75) performed a systematic review and meta-analysis of 13 trials (n = 17,627, of whom 8,163 were patients with type 2 diabetes receiving thiazolidinediones and 9,464 were patients receiving control therapy) that had follow-up periods of 1-5.5 years. They reported that long-term thiazolidinedione use was associated with the risk of developing serious pneumonia or lower respiratory tract infections (RR, 1.42; 95% CI: 1.09-1.84; p = 0.009). The use of DPP-4 inhibitors was not associated with an increased risk for CAP.

But Gooben et al (74) in a systematic review and meta-analysis of 39 RCTs with DPP4Is in diabetic patients (n = 18,491, comparator mostly placebo), did not show an increased risk of all-cause infection (relative risk (RR) = 0.98 (95% CI 0.93–1.05)) or URTS (RR = 0.97 (95% 0.83–1.14)). Similarly, a pooled analysis of 25 clinical studies (n = 14,611) with sitagliptin vs. comparator (mostly placebo) in T2DM patients, showed no increased risk of pneumonia (difference in incidence rate (IR) per 100 patient years between sitagliptin and comparator 0.2 (95% CI -0.2 to 0.5) (75).

Eventually,, large epidemiological databases can be useful tools to evaluate the association of specific antidiabetic drugs with the incidence of CAP, as have shown with other medications(for example PPIs).

4. Summary

This review confirms that treatment with ICSs, PPIs, AAPs, or some oral antidiabetic drugs increases the risk for pneumonia. Use of either TAPs or AAPs is associated with a two- to three-fold increased risk for pneumonia in a dose-dependent manner, with AAPs often associated with a higher risk for pneumonia compared to conventional agents. The frequent use of PPIs, especially in the elderly population, has been linked to an increased risk for pneumonia in a time-dependent manner. Meanwhile, there is now a body of evidence that links ICS use to pneumonia, especially in COPD patients, in a dose-related way, although this is not associated with mortality. Given the potential risk for pneumonia, clinicians should exercise caution when prescribing these drugs for patients with specific indications.

5. Expert opinion

This review provides a comprehensive compilation of data on the risk of developing pneumonia when taking pharmacotherapeutic agents for specific comorbidities.

(1) An increased risk for pneumonia with ICS use in COPD has been reported in both RCTs and observational studies. Despite the number of studies reporting this association, there are still many unresolved issues regarding the link between ICS use and pneumonia in patients with COPD (e.g., class effect, dose effect, influence on mortality, and underlying mechanisms). One possible explanation for the ICS-associated increased risk for pneumonia is that the combination of impaired macrophage function and an altered respiratory microbiome might provide conditions in the lung that favor the development of pneumonia.

Despite these many observations, lingering questions remain. There are doubts about the true incidence of this event in the trials. Is ICS use and pneumonia real or an epiphenomenon (ie, are patients who have more severe COPD and use ICSs more frequently more likely to experience pneumonia simply because of their baseline COPD)?

Moreover, the studies discussed in this review had several methodological limitations; were largely focused on pneumonia events documented as adverse events not as primary outcome ;not using predefined diagnostic radiographic criteria for pneumonia and not including head-to-head comparisons of the different types of ICS (77).

Indeed, the European Medicines Agency's Committee for Medicinal Products for Human Use has stated that there is no difference in the risk for respiratory adverse events for the different classes of ICSs (78).

The benefits of COPD therapy that counterbalance any associated risks may change with time. According to global guidelines for COPD treatment, ICS in combination with a LABA is appropriate for patients with a higher risk for COPD, defined as GOLD stage 3 or 4, and/or frequent exacerbations (79).

Strategies to reduce the risk for pneumonia in COPD patients include withdrawing or reducing the dose of the ICS. As WISDOM study recommend ICS withdrawal is safe if patients are maintained on maximum bronchodilator therapy (80). The need for long-term corticosteroid therapy or using it at a minimally effective dose should be re-evaluated. The identification of specific risk factors for pneumonia could provide a more accurate risk–benefit assessment of ICS treatment in COPD patients. Among the COPD patients treated in the UK, the incidence of CAP is increased in specific subpopulations, particularly those with older age, greater COPD severity, prior CAP episodes, and certain co-morbid conditions (81).

Identifying markers of clinical response to ICSs, such as sputum eosinophils, might enable the targeting of ICS to COPD patients who will benefit, thereby reducing the overall incidence of adverse effects such as pneumonia (77, 82). It is quite difficult to understand the real magnitude of the side effects induced by ICSs given that COPD is associated with several comorbidities, although the role of ICS must always be taken into account.

During the 5 years of follow-up in a case-control study published in 2013, 123 out of 870 (14%) current ICS users had recurrent pneumonia compared to 395 out of 4,603 (9%) participants who had never used ICS (adjusted OR, 1.90; 95% CI: 1.45–2.50; $p < 0.001$; number needed to harm = 20) (83).

Observational studies (81,84,85) and meta-analyses (25, 27) have also shown no significant increases in pneumonia-related mortality in ICS users probably due to reduced non-specific inflammation and decreased neutrophil influx into the lungs. In any case, there is an obvious need for prospective trials to define the dose-dependent risk for pneumonia associated with ICSs and whether the risk varies between the different ICSs.

(2) The association between the use of atypical antipsychotics and the risk for CAP has been explored by epidemiological cohort and case–control studies (86). Antipsychotic drugs are associated with an increased risk for fatal or non-fatal pneumonia in a dose-dependent manner, the risk being high soon after the beginning of treatment (57). Antipsychotic drugs with a higher affinity for histamine H1 receptors are linked to an increased risk for pneumonia. The varying antihistaminergic and muscarinic effects of the different APs may play a major role in the relative risk profile of developing pneumonia. For example, olanzapine has been reported to show a higher affinity for histaminergic and muscarinic receptors than quetiapine (57,87).

In the review of Sultana et al two targets, thromboxane A2 receptor (TBXA2R) and platelet activating factor receptor (PTAFR) were found to be novel AP target receptors potentially associated with pneumonia in relation to the antipsychotics (88). Biological pathways constructed using Cytoscape identified plausible biological links potentially leading to pneumonia downstream of TBXA2R and PTAFR.

It is difficult to explore the relationship between antipsychotics and pneumonia since patients with dementia already have a higher risk for aspiration pneumonia. The methodological issue protopathic bias, as delirium is a prodromal symptom of pneumonia for which antipsychotics may be prescribed; therefore, antipsychotic use may appear to be associated with pneumonia, but in reality, is not. Additionally, most studies investigated APs by class rather than by individual drug, with a few exceptions.

As pneumonia associated with antipsychotic medication in elderly patients is more likely to occur at higher dosages, it is important to start therapy with the lowest dosage possible, followed by careful dose titration. The risk seems to peak at the beginning of treatment (e.g., 7-30 days) and dissipates over time for both conventional and atypical APs.

The increased risk for pneumonia not only applies to elderly individuals, but also to younger patients, although more data are required to confirm the latter. Subgroup analysis failed to show significant differences in the risk for pneumonia between patients with psychiatric diagnoses (schizophrenia and bipolar disorder) and those with mainly cognitive impairment or dementia (88).

In general, the lowest possible dose of antipsychotics should be prescribed. Whenever possible, concomitant administration of antipsychotics with other neuropsychiatric drugs that have a sedative effect (i.e., opioids and benzodiazepines) or anticholinergic properties (i.e., tricyclic antidepressants) should be discouraged or limited to short periods with careful observation.

Further research should provide more details on individual antipsychotics, doses with the lowest risk for developing pneumonia, and the role of the severity of dementia and other possible risk factors as functionality status of the

patients (mobility, dressing and

accommodation) in the association between antipsychotic medication and pneumonia (89).

(3) Observational studies and meta-analysis demonstrate a positive association between PPI use and the risk of CAP. As Eom et al. (49) reported in their meta-analysis, the most striking increase in the PPI-associated prevalence of pneumonia was observed in the first week of PPI use, with about one case of hospitalized pneumonia observed in every 200 patients on PPIs.

PPI therapy may lead to pneumonia both through acute pH dysregulation and alteration of the gut microbiome. The risk for pneumonia is the highest during the first month of therapy, which is the time during which the aerodigestive microbiome might be in greatest flux (90). De Jager et al. concluded that PPI therapy was associated with an approximately two-fold increased risk of developing CAP, possibly as a result of *S. pneumoniae* infection (91). However, a study of the causative microorganism of CAP in patients receiving PPIs did not show an increase in the frequency of either oropharyngeal or gastrointestinal bacteria (92). Another possible explanation could be the immunomodulatory effects of PPIs. Omeprazole and lansoprazole have been shown to inhibit the expression of adhesion molecules on neutrophils, indicating that PPIs may reduce adequate transmigration of leukocytes to sites of inflammation (92). Future studies should employ a rigorous definition of CAP and assess various doses and durations of PPI treatment to further explore the association between PPI use and CAP in specific populations.

6. Conclusion

Treatment with ICSs, PPIs, and antipsychotics, especially atypical antipsychotic drugs, is associated with the risk of developing pneumonia. An increased risk for pneumonia with ICS use in COPD was first described in 2007 and has been subsequently reported in RCTs, observational studies, and meta-analyses. Paradoxically, ICS use is associated with reduced mortality in COPD. Regarding antipsychotic medication, the risk for pneumonia is similar among different age groups, increasing in a dose-dependent manner and in the early phases of treatment for both typical and atypical antipsychotic drugs. Given the morbidity and mortality associated with CAP and the extent of PPI use, identification of any risk associated with PPI use is critical for risk stratification and modification where possible. The association of oral antidiabetics with pneumonia needs to be further examined. The current review provides clinical information that can be used to establish preventive interventions for CAP in adults, especially with regards to prescribed drugs.

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Table 1. Studies examining the risk for CAP in COPD patients treated with ICSs

Authors	Study Period	Design	Setting	Population	Outcome	Exposure	Main Findings: RR or Incidence	Dose effect
Calverley P et al¹⁴ TORCH Trial	2000-2006	RCT	Outpatients 44 centers in 42 countries	Patients 40-80 years old with moderate-severe COPD(N=6,112)	Mortality	FC (1,000 µg) SFC (1,000 µg)	1.52 (95% CI: 1.32-1.76)	NA
Anzueto A et al¹⁷	2007-2008 1 year	RCT	Outpatients	Moderate to severe COPD(N=782)	Overall mortality Pneumonia	FC (500 µg)	7% vs. 2% (LABA)	NA
Kardos P, et al¹⁸	2002-2003 44 weeks	RCT	Outpatients 95 centers in Germany	Severe COPD pts with history of exacerbations (n=994)	COPD exacerbations Pneumonia side effect	SFC (1000 µg)	4.6% vs. 1.43% LABA)	NA
Sharafkhaneh A et al²².	2007-2009 (1 year)	RCT	Outpatients	patients >40 years with COPD moderate to severe, with an exacerbation/year(N=1,219)	Pneumonia & Mortality	FBD (320 µg and 160 µg)	6.4% (320 µg) vs. 4.7% (160 µg) vs. 2.7% (LABA)	NS

Dransfield M et al. ⁸²	2011-2012 (12 weeks)	RCT	Outpatients	Patients >40 years, moderate to severe COPD(N=1860)	Pneumonia Pneumonia Mortality	VFFg (50 µg, 100 µg, and 200 µg)	7.3% vs. 3.4% (LABA)	NS
Wedzicha J et al ¹⁵ .	2003-2004 2 years	RCT	Outpatients	Patients>40 years, severe - very severe COPD (N=1,323)	Pneumonia	SFC (500 µg) LAMA (18 µg)	1.94 (95% CI: 1.19–3.17)	NA
Crim C et al ³⁴ . (SUMMIT Trial)	2011-2014 3 years	RCT	Outpatients	subjects >40 years with moderate airflow limitation and heightened cardiovascular risk (N=16,568)	Pneumonia Pneumonia mortality	VF (25 µg/100 µg), VI, FF	Not associated	No
Volgemeier C, et al ¹⁹ ILLUMINATE study	2011-2012 26 weeks	RCT	Outpatients 93 centres in 10 countries	Patients age >40 years, GOLD stages II–III, without exacerbations in the previous year (N=523)	Pneumonia mortality	QVA149 110/50 µg once daily SFC 50/500 µg twice daily	0 vs. 1.5%	NS
Ernst P et al. ²⁸	1998-2003 14 years	Nested case-control	Inpatient	COPD patients >65 years (N=40366, n=79344)	Pneumonia (Crude & Adjusted)	All ICS	1.70 (95% CI: 1.63-1.77)	Yes

Suissa S et al. ²¹	1990-2005 Through 2007	Case-control	Quebec health insurance databases	COPD patients, ICS users (N=163,514)	Serious pneumonia event, Mortality	FC, BUD	1.69 (95% CI: 1.63-1.75)	Yes
Joo MJet al ³⁰	1998-2002 4 years	Case-control	Veterans Affairs and Centers for Medicare and Medicaid Services Database	Patients >65 years with a new diagnosis of COPD (N=145586; cases=13995)	Pneumonia Mortality	All ICS	1.38 (95% CI: 1.31-1.45)	No
Mullerova H et al ⁷	1996-2005	Retrospective cohort	General Research Practice Database (GPRD)	A cohort of COPD patients aged >45years (N=40,414)	Risk factors for CAP in COPD patients	All ICS	Not associated	NA
Janson C et al. ²⁹	1999-2009	Retrospective cohort	Swedish National Board of Health and Welfare	COPD patients (N=9,893)	Pneumonia, mortality	FBD, SFC	1.73 (95% CI: 1.57-1.90) vs. 1.74 (1.56-1.94)	NA
Mapel D ³³	2000-2003	Nested case-control	Databases of three large regional managed care organizations	COPD patients (N=5,245)	Pneumonia	All ICS	1.29 (95% CI: 0.96-1.73)	NA

Gau JT et al. ¹⁰	2004-2006	Case-control	A rural community hospital	adults aged >65 years (N=194 Controls: 952)	Pneumonia event	All ICS, atypical antipsychotics and PPIs	2.89 (95% CI: 1.56-5.35)	NA
Festic E et al ³⁶	2009 2 years	prospective cohort	LIPS cohort N=5884	COPD patients taking ICS N=589	Pneumonia hospitalization	All ICS	1.40 (95% CI 0.95–2.09; p=0.093)	NA
DiSantostefano R et al. ³²	2002-2010	Observational cohort	United Kingdom electronic medical records with linked hospitalization	Pneumonia events in COPD patients >45 years were compared among new users of ICS (N=11,555)	Risk of pneumonia	All ICS	1.49 (95% CI: 1.22-1.83)	Yes

ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease; RR, relative risk; FC, fluticasone propionate; SFC, salmeterol plus fluticasone;

Table 2. Studies investigating PPIs as risk factors for pneumonia.

Authors	Study period	Design	Setting	Population	Outcome	Exposure	Main Findings Adj OR
Sugano et al. ³⁹	2007-2009	RCT	47 healthcare institutions	Long-term NSAID users with history of ulcer	Pneumonia	PPIs	Not associated
Laheij RJ et al. ⁴⁰	1995-2002	Nested case-control	Integrated Primary Care Information database	Incident users of IPPs (N=364683, n=5551)	Pneumonia	PPIs	Current use: 1.73 (1.33-2.25)
Gulmez SE et al. ⁴¹	2000-2004	Population based case-control	Government Patient Registries County of Funen, Denmark	Patients with pneumonia; N=7642 Controls=34 176	Pneumonia	PPIs	Current use: 1.5 (1.3-1.7) Past use: 1.2 (0.9-1.6) Initiation: 5 (2.1-11.7)

Sarkar M et al. ⁴⁴	1987-2002	Nested case-control	The General Practice Research Database in the UK	Patients >18 years old, 6 months after pneumonia. PPIs users within 30 days before the index date Cases=80,066 , controls=779881	Pneumonia	PPIs	Initiation 2D: 6.53 (3.95-10.80), 7D: 3.79 (2.66-5.42), 14D: 3.21 (2.46 - 4.18)
Rodriguez LA et al. ⁴³	2000-2005	Case control	Health Improvement Network database	Patients aged 20–79 years with a new diagnosis of pneumonia between 2000 and 2005 (n =7297)	Risk of pneumonia	PPIs H ₂ RAs	RR: PPIs:1.16 (1.03–1.3), H ₂ RAs:0,98(0,8-1,2)
Myles PR et al. ⁴²	2001-2002	Population-based case-control	Health Improvement Network (THIN)	Patients >40 years Old- inpatients or outpatients N=3,709	Pneumonia	statins , ACE inhibitors (ACEI), PPIs, H ₂ RAs	PPIs:1.55 (1.35-1.77) H ₂ RAs:1.14,(0.92–1.40)
Meijvis SCA et al. ⁹⁰	2004-2010	Population-based Case-control	PHARMO Record Linkage System Database and 2	Patients with CAP admitted to hospital cases=430 Controls=2,150	Pneumonia	PPIs	Current use: 3,1 (1.4-7.1)

			hospitals in Netherland				
De Jager C e t al⁸⁹.	2007-2010	Prospective cohort	Outpatients	Patients having CAP seen on the emergency care unit (N=463)	CAP from <i>Str.pneum oniae</i> & CAP severity	PPIs	2 (1.22-3.72)
Ho SW et al⁴⁵	2009-2013	Retrospectiv e population- based cohort	Taiwanese National Health Insurance Research Database	Adult patients aged ≥40 years with new-onset dementia Cases:786 Control:786	Pneumonia	PPIs	HR = 1.89;1.51–2.37)

H2RAs = histamine2-receptor antagonists, PPIs:Proton Pump Inhibitors; CI = confidence interval, CAP: community acquired pneumonia

Table 3. Observational studies investigating the risk for pneumonia associated with antipsychotic medication

Authors	Study design	Setting	Population	Outcome	Exposure	Main findings
Knol W et al. ⁵⁸	Nested case-control	Dutch PHARMO database	Patients > 65 years newly treated with Aps(N = 22,944;n = 543 cases)	Hospital admission due to pneumonia	AAPs orTAPs (non-use as comparator)	Adj OR: Current use of AAPs: 3.10 (1.89-5.07) TAPs: 1.5 (1.2-1.9)
Barnett MJ ⁵⁶	Retrospective cohort	US Veterans Administration database	Hospitalized for CAP (N = 16,931)	In-hospital mortality	AAPs or TAPs (no use Of neuropsychiatric drugs as comparator)	Adj OR:TAPs: 1.5 (1.0-2.2) AAPs: 1.2 (1.0-1.5)
Trifiro G et al ⁵⁷ .	Nested case-control	Dutch general practice database (Integrated Primary Care Information)	Patients > 65 years newly treated with APs (N=258)	Fatal and non-fatal CAP	AAPs or TAPs (past use of any AP as comparator)	Adj. OR: fatal/non-fatal pneumonia: AAPs: 2.61 (1.48–4.61) TAPs: 1.76 (1.22–2.53) Fatal pneumonia: AAPs: 6.0 (1.5–24.0) TAPs: 1.7 (0.8–3.9)
Gau GT et al ¹⁰ .	Case-control	Rural community	USA, patients >65 years (N=194)	CAP	AAPs (non-use as comparator)	Adj.OR: AAPs:2.26 (1.23-4.15)

		hospital in Ohio (US)				
Pratt N et al. ⁶³	Self-controlled case series	Australian Government Department of Veterans' Affairs Health Care Claims Database	Veterans/spouses aged >65 years (N = 8,285)	Hospitalized for hip fracture & pneumonia	TAP & AAP	<p>-TAPs at 1 week: 1.51 (1.07-2.14)</p> <p>-TAPs at 2-8 weeks: 1.62 (1.37-1.92)</p> <p>-TAPs at 9-12 weeks: 1.69 (1.32-2.16)</p> <p>-TAPs > 12 weeks: 1.63 (1.36-1.96)</p> <p>- AAPs at 1 week: 1.73 (1.31- 2.29)</p> <p>- AAPs at 2-8 weeks: 1.70 (1.48-1.95)</p> <p>- AAPs at 9-12 weeks: 1.67 (1.37-2.04)</p> <p>- AAPs > 12 weeks: 1.70 (1.51-1.93)</p>
Huybrechts KF et al. ⁶⁴	Retrospective cohort	Medicaid-- Medicare, Minimum	Nursing home residents > 65 years who initiated antipsychotic	myocardial infarction, cerebrovascular	AP & TAP	<p>Adj. HR</p> <p>- TAPs: 0.81 (0.65-1.01)</p>

		Data Set and Online Survey Certification and Reporting data	treatment in nursing home (N=83,959)	events, serious bacterial infections (including pneumonia), and hip fracture within 180 days of antipsychotic initiation		- aripiprazole: 0.99 (0.72-1.35) - olanzapine: 0.94 (0.84-1.05) - quetiapine: 0.91 (0.80-1.03)
Aparasu RR et al⁵⁹.	Retrospective cohort	Medicaid-Medicare data	Nursing home elderly patients who are new users of AAPs(N=49904)	Pneumonia	TAPs (AAPs as comparator)	Adj. HR < 50 days: 1.17 (0.83-1.66) 50 - 180 days: 1.36 (0.87 - 2.14)
Kuo CJ et al⁶¹	Nested case-control study	National Health Insurance Research Database in Taiwan	>1 psychiatric admission between 2000 and 2008(schizophrenia), age>18 years old Cases :n = 1741 Controls: 6949	Risk of hospitalization for Pneumonia	Second generation Aps by class; AAPs by class	Current use clozapine adjRR : 5.3;18,(2.62–3.86)
Metha S, et al⁶⁵	Retrospective cohort study	Medical Outcomes Research for	New users of	Pneumonia risk	AAP: olanzapine, risperidone,	HR:

		Effectiveness and Economics Registry (MORE2 Registry)	atypical antipsychotics (≥65 years) (N=92 234)		quetiapine, ziprasidone, or aripiprazole	risperidone :1.14, (I 1.10–1.18) and olanzapine : 1.10, (1.04–1.16) compared with the use of quetiapine.
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Risk estimates

Adj, adjusted; AAPs, atypical antipsychotics; APs, antipsychotics; TAPs, typical antipsychotics; CAP: community acquired pneumonia;

HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, rate ratio.

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Table 4. Studies investigating the risk for pneumonia associated with oral antidiabetics

Authors	Design	Setting	Population	Outcome	Exposure	Main Findings
Gorricho et al⁷²	Nested case-control	Spanish general practice research database	Cases were people diagnosed of T2DM, aged >18 years and with a validated diagnosis of CAP between 2002-2013 N=76,009 T ₂ DM & N=1803	Pneumonia	OAD	thiazolidinediones+metformin adj OR=2.48(1.40–4.38) DPP-4 inhibitors: NA
Willemsen MJ et al⁶⁸	Nested case-control	WHO's Adverse Drug Reactions database	305,415 suspected ADRs involving antidiabetic drugs in 106,469 case reports	ADRs classified as an infection.	OAD	SU derivatives: 1.1 (0.9–1.3) TZDs: 1.3 (1.1–1.5) DPP-4 : 2.3 (1.9–2.9)
Failie JL et al⁷⁰	Nested case-control	UK Clinical Practice Research Datalink	New users of antidiabetic drugs (N=49653)	Hospitalization for pneumonia	DPP-4 Inh.	Adj OR:0,80(0,5-1,29)

Mor A et al ⁷¹	Population-based cohort	General practice & hospitals in Denmark	Patients with type 2 diabetes and initiated pharmacotherapy	Pneumonia: community and hospital acquired	Initial GLDs	Sulfonylurea inh.:HR:1,12(1,08-1,16)
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Wvan der Zanden R, et al⁶⁹	Population- Based Cohort	CPRD	>18 years with DM receiving NIAD 211,049 NIAD users	Pneumonia	NIAD	current use of DPP4Is: NA
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OAD: oral antidiabetic drugs, GLDs: glucose lowering drugs, ADR: adverse drug reaction,

DPP-4 I: dipeptidyl peptidase inhibitors; SU: sulfonylurea; TZD: thiazolidinediones

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