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**Chronic Obstructive Pulmonary Disease** FALL 2014 Volume 5 Number 1



**Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study.**  
*Eur Respir J* 2012 Oct; 40(4):830-836. Epub 2012 Mar 22

The efficacy and safety of two doses of aclidinium bromide were evaluated in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

**Methods:** In this 24-week, double-blind trial, patients were randomized to twice-daily aclidinium (200 mg or 400 mg) or placebo. The primary efficacy end-point was change in trough forced expiratory volume in 1 s (FEV1) at week 24. Other end-points included peak FEV1, health status (St George’s Respiratory Questionnaire; SGRQ) and dyspnea (Transitional Dyspnoea Index; TDI).

**Results:** In total, 828 patients were randomized. At week 24, significant improvements from baseline were observed with aclidinium 200 mg and 400 mg versus placebo for trough FEV1 (99 and 128 mL; both p, 0.0001) and peak FEV1 (185 and 209 mL; both p, 0.0001). Peak FEV1 improvements on day one were comparable with week 24. Aclidinium 200 mg and 400 mg produced significant improvements over placebo in baseline-adjusted mean SGRQ total score (-3.8 and -4.6 units; p, 0.001 and p, 0.0001) and TDI focal score (0.6 and 1.0 units; p, 0.05 and p, 0.001) at week 24. With both aclidinium doses, the incidence of anticholinergic adverse events was low, and similar to placebo.

**Conclusion:** Twice-daily aclidinium significantly improved bronchodilation, health status and dyspnea, and was well tolerated in patients with COPD.

**Source:** Paul W. Jones, Dave Singh, Eric D. Bateman, Alvar Agusti, Rosa Lamarca1, Gonzalo de Miquel, Rosa Segarra, Cynthia Caractae and Esther Garcia Gil.

PMID: 22441743 [PubMed - indexed for MEDLINE]

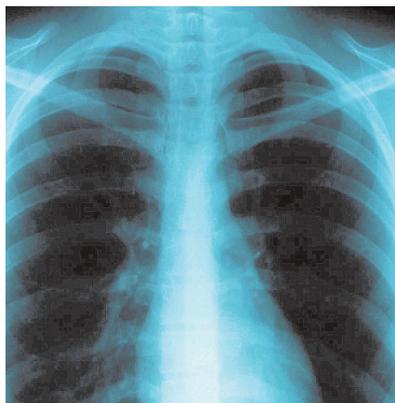
The COPD Digest is published quarterly by Chronicle Information Resources Ltd. for COPD Canada. Each issue reviews recently published (PubMed) clinical **abstracts** with **comments** from **Dr. Kenneth R. Chapman, MD, MSc, FRCPC, FACP**, Director of the Asthma and Airway Centre, University Health Network, Toronto





DIALOGUE

**Bronchodilators are considered foundational** pharmacotherapy in COPD and anticholinergic bronchodilators have been used in this role for decades, either as monotherapy or combined with beta<sub>2</sub> agonists. Of the several new anticholinergic bronchodilators becoming available in Canada, aclidinium bromide is distinctive in several important ways. First, it is approved for twice daily administration not once daily. Although this may be a possible compliance disadvantage, the use of the evening dose of aclidinium may offer better early morning lung function as compared to once daily agents, a finding reported in at least one comparative study with tiotropium. Second, aclidinium is rapidly hydrolyzed in serum so that its potential for systemic anticholinergic side effects is thought to be less than currently available anticholinergic agents. Finally, it is delivered via a novel inhalation device, the Genuair®, which offers built-in feedback mechanisms to optimize patient inhalation technique. In this pivotal trial, Jones and colleagues report that 200 and 400 mcg doses of aclidinium achieve similar and significant improvements in lung function. More important, the patient reported outcomes including health status and relief of dyspnea were improved significantly, not only in a statistical sense but in a clinical sense. Aclidinium offers a useful treatment option for patients intolerant of usual anticholinergic side-effects, particularly if they are already using twice-daily medications.



DIGEST

## Guidance on handheld inhalers in asthma and COPD guidelines

*Respir Med* 2014 May; 108(5):694-700.

doi: 10.1016/j.rmed.2014.02.013. Epub 2014 Mar 1

Inhaled therapy is the cornerstone of pharmacotherapy in patients with asthma and chronic obstructive pulmonary disease (COPD). Appropriate inhalation device selection is as important as drug choice but device-specific guidance appears to be lacking.

**Methods:** To quantify the level of inhalation-device recommendations in clinical guidelines, a review was conducted by hand-searching national and international asthma and COPD guidelines (Global Initiative for Asthma [GINA] and Global initiative for chronic Obstructive Lung Disease [GOLD] guidelines) and an international guideline on device selection (the American College of Chest Physicians/American College of Asthma, Allergy, and Immunology [ACCP/ACAAI]). For each guideline, the number of pages, tables/figures and references relating to inhalation devices was identified.

**Results:** GINA and GOLD guidelines contain very little inhalation device-specific guidance beyond recommendations for demonstrating and testing correct inhalation technique: <2% of pages or references and <3% of tables/figures are dedicated to devices. Device-related content in the ACCP/ACAAI device selection guideline was considerably higher with 54% of pages, 88% of tables/figures and 82% of references, respectively. Results in national guidelines reflect those on international guidelines.

**Conclusions:** These results indicate that there is a considerable lack of clear and specific guidance regarding inhalation devices in current asthma/COPD guidelines. More robust studies on the impact of inhalation devices are needed to increase the number of evidence statements and recommendations regarding inhalation devices.

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**Source:**

Dekhuijzen PN, Bjermer L, Lavorini F, Ninane V, Molimard M, Haughney J.

PMID: 24636812 [PubMed - in process]



DIALOGUE

**We rely upon inhaled medications** to treat our patients with COPD. Such medications are being made available in an increasing range of proprietary devices including multi-dose dry powder inhalers, single dose dry powder inhalers, the familiar metered dose inhaler or pressurized aerosol inhaler and soft mist inhalers. We also know that not all patients can

use all types of inhaler and that patient mishandling of devices is common. Moreover, physicians and health care providers are often unfamiliar with the correct technique for using such devices and either fail to teach their patients or teach them incorrectly. Nonetheless, Dekhuijzen and colleagues report that a survey of international and national guidelines for asthma and COPD shows little attention is paid to this topic. In their online supplement describing national guidelines, these investigators found that national societies most often pattern national guidelines on the GINA and GOLD guidelines so that just 2 to 3% of the guideline material referred to inhaler issues. The role of guidelines is unclear and they often fail to change practice for the better and to improve patient outcomes. By neglecting such a fundamental element of respiratory care, these international guidelines cannot hope to improve outcomes particularly for the 80% of asthma and COPD patients cared for in non-specialty practices where trained educators are less likely to be found.



## Tiotropium Respimat inhaler and the risk of death in COPD

*N Engl J Med* 2013 Oct 17; 369(16):1491-1501.

DIGEST

doi: 10.1056/NEJMoa1303342. Epub 2013 Aug 30

Tiotropium delivered at a dose of 5 mug with the Respimat inhaler showed efficacy similar to that of 18 mug of tiotropium delivered with the HandiHaler inhalation device in placebo-controlled trials involving patients with chronic obstructive pulmonary disease (COPD). Although tiotropium HandiHaler was associated with reduced mortality, as compared with placebo, more deaths were reported with tiotropium Respimat than with placebo.

**Methods:** In this randomized, double-blind, parallel-group trial involving 17,135 patients with COPD, we evaluated the safety and efficacy of tiotropium Respimat at a once-daily dose of 2.5 mug or 5 mug, as compared with tiotropium HandiHaler at a once-daily dose of 18 mug. Primary end points were the risk of death (noninferiority study, Respimat at a dose of 5 mug or 2.5 mug vs. HandiHaler) and the risk of the first COPD exacerbation (superiority study, Respimat at a dose of 5 mug vs. HandiHaler). We also assessed cardiovascular safety, including safety in patients with stable cardiac disease.

**Results:** During a mean follow-up of 2.3 years, Respimat was noninferior to HandiHaler with respect to the risk of death (Respimat at a dose of 5 mug vs. HandiHaler: hazard ratio, 0.96; 95% confidence interval [CI], 0.84 to 1.09; Respimat at a dose of 2.5 mug vs. HandiHaler: hazard ratio, 1.00; 95% CI, 0.87 to 1.14) and not superior to HandiHaler with respect to the risk of the first exacerbation (Respimat at a dose of 5 mug vs. HandiHaler: hazard ratio, 0.98; 95% CI, 0.93 to 1.03). Causes of death and incidences of major cardiovascular adverse events were similar in the three groups.

**Conclusions:** Tiotropium Respimat at a dose of 5 mug or 2.5 mug had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 mug in patients with COPD. (Funded by Boehringer Ingelheim; TIOSPIR ClinicalTrials.gov number, NCT0112643).

**Source:** Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, Dusser D, Joseph E, Kattenbeck S, Koenen-Bergmann M, Pledger G, Calverley P; TIOSPIR Investigators.

PMID: 23992515 [PubMed - indexed for MEDLINE]



DIALOGUE

**The TIOSPIR study** was undertaken to address concerns that tiotropium delivered by soft mist inhaler or Respimat® was associated with increased mortality. A meta-analysis reporting this finding had reawakened concerns about the cardiovascular safety of tiotropium. (Singh, S, et al. (2011). "Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials." *BMJ* 342:d315). Singh metaanalysis reported 50% increase in mortality for patients treated with tiotropium in the Respimat® as compared to placebo treated patients. At the highest tiotropium dosage used in this formulation (10 mcg), the mortality was doubled. In the TIOSPIR study, patients were randomized to receive tiotropium via the familiar Handihaler® at the standard dosage of 18 mcg or tiotropium via the Respimat® at either 2.5 or 5 mcg per inhalation. Mortality was similar amongst the three treatment arms. However, there was no placebo treatment arm so that the reassurance of safety is limited to the reassurance that the three treatment arms are associated with similar mortality rates. Given the results of the UPLIFT study showing a trend for reduced mortality in those treated with tiotropium in the Handihaler® as compared to those treated with placebo, this should be a comforting finding. However, subsequent letters to the editor voiced further concerns. Loke and colleagues noted that the higher dose of tiotropium in the Respimat® was associated with an increase in fatal myocardial infarction while Verhamme and colleagues reported that concerns about excess mortality seemed relevant primarily in patients with impaired renal function. It appears that concern about adverse anticholinergic effects with tiotropium will grumble on. Some effects are obvious but relatively benign such as dry mouth. Urinary retention is more concerning but most concerning is the issue of adverse cardiovascular events. Care should be taken when prescribing to those predisposed—those with prostatic symptoms and those with impaired renal function, for example.



DIGEST

## Multicentric study on beta-blocker use and relation to exacerbations in COPD

*Respir Med* 2014 May; 108(5):737-444.

doi: s.2014.02.009. Epub 2014 Feb 20

Chronic obstructive pulmonary disease (COPD) is frequently associated with chronic heart failure (CHF) or coronary artery disease (CAD). In spite of the recommendation to use beta-blockers (BB) they are likely under-prescribed to patients with concurrent COPD and heart diseases.

**Methods:** To find out the prevalence of use of BB, 256 COPD patients were consecutively recruited by pulmonary physicians from 14 hospitals in seven regions of Spain in their outpatient offices if they had a diagnosis of COPD, were not on long-term oxygen therapy, had CHF or CAD, and met the criteria for BB treatment.

**Results:** In patients with indication 58% (95% CI, 52-64%) of the COPD patients and 97% of the non-COPD patients were on BB ( $p < 0.001$ ). In patients with COPD, several factors were independently related to at least one visit to the emergency room in the previous year such as use of BB, adjusted OR=0.27 (95% CI 0.15-0.50), GOLD stage D, OR=2.52 (1.40-4.53), baseline heart rate >70, OR

=2.19 (1.24-3.86), use of long-acting beta<sub>2</sub>-agonists OR=2.18 (1.29-3.68), previous episodes of left ventricular failure OR=2.27 (1.19-4.33) and diabetes, OR=1.82 (1.08-3.38).

**Conclusions:** We conclude that, according to what is recommended by current guidelines, BB are still under-prescribed in COPD patients. COPD patients with CHF or CAD using BB suffer fewer exacerbations and visits to the ER. GOLD stage, use of long-acting beta<sub>2</sub>-agonists, baseline heart rate and comorbidities are also risk factors for exacerbations in this population.

**Source:** Puente-Maestu L, Calle M, Ortega-González A, Fuster A, González C, Márquez-Martín E, Marcos-Rodríguez PJ, Calero C, Rodríguez-Hermosa JL, Malo de Molina R, Aburto M, Sobradillo P, Alcázar B, Tirado-Conde G; GEMEPOC Group.

PMID: 24635914 [PubMed - in process]



DIALOGUE

**This multicentre Spanish paper** is the latest to show that patients with COPD are often denied the considerable benefits of beta blocker therapy even when warranted by serious co-morbidities such as congestive heart failure. The avoidance of beta blockers likely stems from ongoing confusion about distinguishing asthma from COPD. Although both are airflow obstructive diseases, their characteristics contrast markedly. Spirometry is the most useful tool for distinguishing the diseases. In asthma, the obstruction is variable and with effective therapy, should resolve entirely. In COPD, the obstruction is persistent and despite some improvement with therapy, is never completely reversed. The former disease is corticosteroid responsive; the latter is much less so. We know that beta blockers can induce marked wheezing in patients with asthma; the same is not true in COPD. One must acknowledge the presence of ACOS or asthma/COPD overlap syndrome but such patients are likely no more than 15 or 20% of the COPD population. If there is concern that the overlap is present, a cardioselective beta blocker could be introduced cautiously in low dosage with spirometry done before and after. Parenthetically, Phase III bronchodilator studies in COPD provide limited information on this issue. If a beta<sub>2</sub> agonist bronchodilator is to be tested, the concurrent use of beta blockers is typically an exclusion criterion. Our understanding of beta blocker use or avoidance in COPD comes almost entirely from such real world observational studies as that of Puente-Maestu and colleagues.



DIGEST

## Comorbid pulmonary disease and risk of community-acquired pneumonia in COPD patients

*J Tuberc Lung Dis* 2013 Dec;17(12):1638-1644.  
doi: 10.5588/ijtld.13.0330

Risk of pneumonia in chronic obstructive pulmonary disease (COPD) patients due to comorbid pulmonary disease is not well understood.

**Objective:** To compare factors associated with risk of community-acquired pneumonia (CAP) in COPD patients for those with and without lung cancer, bronchiectasis and/or history of active tuberculosis.

**Design:** Retrospective chart review of patients diagnosed with COPD (forced expiratory volume in 1 second/forced vital capacity < 0.70) between 2006 and 2010, including patient characteristics, occurrence of CAP and type of inhalation treatment. Pneumonia-free survivals were assessed using Kaplan-Meier curves. Factors associated with CAP were assessed using Cox's proportional hazard regression and expressed as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs).

**Results:** Of 2,630 patients, 402 (15.3%) developed CAP during follow-up. The likelihood of CAP increased with increased age (aHR 1.03, 95%CI 1.02-1.04), lower

body mass index (BMI; aHR 0.97, 95%CI 0.95-1.00), lung cancer (aHR 3.81, 95%CI 2.88-5.05), bronchiectasis (aHR 2.46, 95%CI 1.70-3.55) and inhaled corticosteroid (ICS) containing treatment (aHR 1.60, 95%CI 1.30-1.96). ICS-containing treatment was associated with increased risk of CAP only for patients without comorbid pulmonary disease (aHR 1.68, 95%CI 1.30-2.17).

**Conclusion:** For COPD patients: 1) increased age, low BMI, lung cancer and bronchiectasis may increase the risk of CAP, and 2) without respiratory comorbid disease, ICS use increases the risk of CAP.

**Source:** Lin SH, Ji BC, Shih YM, Chen CH, Chan PC, Chang YJ, Lin YC, Lin C.

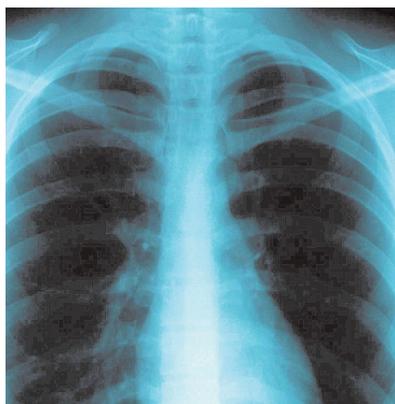
PMID: 24200282 [PubMed - in process]



DIALOGUE

**The downside of inhaled corticosteroid (ICS)** use in COPD is now well-known with much of the attention focussed on the increased risk of pneumonia. It's generally agreed that patients with COPD have a 60% greater likelihood of developing pneumonia if they use ICS than if they do not. The risk appears within a few months of

beginning such therapy and, as far as is known, persists indefinitely. Similarly, at least three reports have shown an increased risk of reactivation tuberculosis in patients with COPD when they are treated with ICS. The absolute risk is small in countries where tuberculosis is uncommon and large in countries where TB is endemic. In South Korea, investigators showed that ICS use increased the TB risk independent of pre-existing chest x-ray changes but the presence of scarring on a chest X-ray compatible with previous TB greatly magnified the risk of TB reactivation. This retrospective study by Lin and colleagues looked for similar cofactors that might magnify the risks of ICS use with respect to community acquired pneumonia. They found that the presence of lung cancer or bronchiectasis increased the likelihood of pneumonia in COPD patients but that ICS use did not increase the risk further in these already high-risk patients. They did confirm, however, that even when COPD was not complicated by coexisting lung cancer or bronchiectasis, ICS increased the risk of community-acquired pneumonia.



DIGEST

## The association between inhaled long-acting bronchodilators and less in-hospital care in newly-diagnosed COPD patients

*Respir Med* 2014 Jan; 108(1):153-161.

doi: 10.1016/j.rmed.2013.08.003. Epub 2013 Aug 30

Although the efficacy of inhaled long-acting bronchodilators has been well documented in randomized controlled studies, whether similar effects are obtained in real-life clinical practice is not clear. In this study, we analysed the effect of inhaled long-acting bronchodilators in newly-diagnosed COPD patients.

**Methods:** The Korean Health Insurance Review and Assessment Service databases were used. Participants  $\geq 40$  years old who had not been diagnosed with COPD between 2007 and 2008 but were diagnosed and prescribed COPD medication in 2009 were designated as newly-COPD diagnosed patients. Patients were divided into three groups based on the use of bronchodilators, an inhaled long-acting bronchodilator (LA-B), an inhaled short-acting bronchodilator (SA-B) and an oral medication (OM) group.

**Results:** A total of 77,480 newly-diagnosed COPD patients with a mean age of 68.5 years, among which 43,530 (56.2%) were men, were included in the study. Emergency Room visits and hospitalization were associated with SA-B group, male gender, older age, Medicaid coverage, tertiary health care centre visits and higher comorbidities. Multivariate analysis showed that the SA-B group was associated with more ER visits, recurrent ER visits, hospitalisation and recurrent hospitalization (adjusted ORs [95% confidence intervals]=4.32 [3.93-4.75], 6.19

[5.24-7.30], 5.04 [2.95-3.39], and 8.49 [7.67-9.39], respectively) compared with the LA-B group. Medical utilization cost was also higher in the SA-B group.

**Conclusions:** Inhaled long-acting bronchodilator use was associated with lower rates of hospitalization, fewer ER visits and lower medical costs in newly-diagnosed COPD patients in real-life clinical practice.

**Source:** Kim J, Kim K, Kim Y, Yoo KH, Lee CK, Yoon HK, Kim YS, Park YB, Lee JH, Oh YM, Lee SD, Lee S.

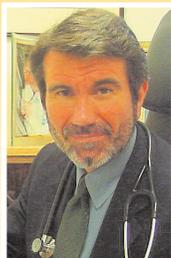
PMID: 23993445 [PubMed - in process]

**COPD is considered by CIHI** (Canadian Institute for Health Information) to be the ambulatory care sensitive chronic disease responsible for the highest



DIALOGUE

number of hospitalizations today. With the continuing rise in COPD prevalence, this grim statistic is unlikely to change in the near future. Payers are looking at many strategies to contain the inevitably rising costs of these hospitalizations but all governments should take the time to consider these observations from Korea. Patients with recently diagnosed COPD were five times more likely to be hospitalized for COPD exacerbations if their treatment was with short-acting bronchodilators rather than long-acting bronchodilators. Emergency room visits, repeat emergency room visits and repeat hospitalizations were similarly increased. This observation cannot prove a cause and effect relationship; we don't know why some patients received short-acting rather than long-acting bronchodilators and it's possible some confounding issue might offer the explanation. But randomized studies that have compared long-acting to short-acting bronchodilators have found that the better sustained bronchodilator effect of the longer-acting agents is typically associated with fewer exacerbations if the trials are of sufficient size and duration and the exacerbation endpoint tracked. Unfortunately, many governmental payers have attempted to reduce costs of care by limiting access to slightly more expensive bronchodilators. This may be false economy if patients require more urgent care as a result.



**Dr. Kenneth R. Chapman** is Director of the Asthma and Airway Centre of the University Health Network, President of the Canadian Network for Respiratory Care and Director of the Canadian Registry for Alpha 1 Antitrypsin Deficiency. A graduate of the University of Toronto and a former member of the faculty at Case Western Reserve University, he is now a Professor of Medicine at the University of Toronto.

We invite your comments. Please mail comments to: The COPD Digest, c/o COPD Canada, 555 Burnhamthorpe Rd., Suite 306; Toronto, Ont. M9C 2Y3. Or you can e-mail questions to: [copd.canada@gmail.com](mailto:copd.canada@gmail.com)

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