Drug, Healthcare and Patient Safety

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Safety and tolerability of inhalational anticholinergics in COPD

This article was published in the following Dove Press journal:
Drug, Healthcare and Patient Safety
7 March 2013
Number of times this article has been viewed

Amir Sharafkhaneh[1,2]
Hashir Majid[3]
Nicholas J Gross[4]

[1]Baylor College of Medicine, Department of Medicine, Houston, USA; [2]Sleep Disorders Center, Michael E DeBakey VA Medical Center, Houston, USA; [3]Aga Khan University, Karachi, Pakistan; [4]Stritch School of Medicine Illinois, St Francis Hospital, Hartford, USA

Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. With the significant toll of the disease, more resources have been invested in developing new treatment modalities. Among these medications, inhalational anticholinergics are widely used for the management of stable COPD. The newer agents, with longer half-lives and better safety profiles, have emerged and helped to improve management of COPD patients. The available data from randomized clinical trials support use of these agents. Multiple randomized clinical trials show safety and efficacy of the newer long-acting inhaled anticholinergics, including tiotropium and aclidinium. A recent meta-analysis of tiotropium delivered with Respimat® raised some safety concerns. A large trial, comparing different doses and delivery methods of inhaled tiotropium, is ongoing to determine the effect on mortality. As clinical trials may not comprehensively represent the entire COPD population, caution should be exercised when these agents are used in higher-risk populations, like individuals with cardiac arrhythmias or urinary obstruction. In this publication, we review the safety of inhalational anticholinergics.

Keywords: tiotropium, cardiovascular side effects, arrhythmia, stroke, aclidinium

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating condition that results in significant morbidity and mortality. Patients with COPD present with dyspnea, cough, sputum production, decreased exercise capacity, and fatigue. COPD not only affects patients physically, but also significantly affects their quality of life. The course of COPD is complicated by episodes of acute exacerbations, which are associated with increased mortality, worse quality of life, and faster lung function decline. COPD is a major public health problem throughout the world. Currently, there are an estimated 12.6 million individuals affected by COPD and it is the sixth most prevalent chronic disease condition, right after diabetes mellitus and asthma in the US. Moreover, recent data indicate that as high as 45% of patients who suffer from COPD are not yet diagnosed. COPD is also a major cause of mortality. Currently, COPD is the third leading cause of death in the US.[1,2]

Physiologically, COPD is characterized by expiratory airflow limitation that is partially reversible.[3] This airflow limitation results in hyperinflation which causes progressive dyspnea and exercise limitation. The dyspnea results in a decline in physical activity, causing worsening of respiratory status due to deconditioning.[4] Current management guidelines consider COPD as a "preventable and treatable" disease.[3,5] The American Thoracic Society/European Respiratory Society outlines clear goals for the management of patients with COPD.[3,5] Treatment goals include improving symptoms,

Correspondence: Amir Sharafkhaneh
Baylor College of Medicine, MEDVA Medical Center Bldg. 100 (111i), Houston, Texas, USA 77030
Tel +1 713 794 7668
Fax +1 713 794 7295
Email amirs@bcm.edu

exercise capacity, and quality of life, and reducing complications such as exacerbations, hospitalizations, and mortality. Smoking cessation clearly slows down lung function decline and prolongs life in COPD, while other preventive measures, including influenza and pneumococcal vaccinations, may affect various outcomes positively in patients with COPD.[3,5,6] Long-term oxygen therapy also reduces mortality in COPD patients with resting hypoxemia.[3,5] Bronchodilators are the mainstay of therapy for symptomatic COPD.[7] Inhalational anticholinergic bronchodilators are recommended and have been used extensively throughout the last few decades, either alone or in combination with inhaled beta agonists.[3] In recent years, long-acting anticholinergic agents have played a significant role in the management of COPD. Despite the widespread use of ipratropium and tiotropium in the USA and other areas of the world, some data from the literature cast doubt about the safety of inhalational anticholinergics. Therefore, we review the safety and tolerability of this class of medications.

Inhalational anticholinergics

Inhalational anticholinergics (with antimuscarinic activity) for the treatment of COPD include ipratropium bromide, tiotropium bromide, and oxitropium bromide. Aclidinium bromide is a new, twice-a-day anticholinergic that recently underwent Food and Drug Administration (FDA) review and was approved for the management of stable COPD. All the current medications contain a quaternary ammonium that limits their systemic absorption and penetration across the blood–brain barrier. They also have a longer duration of action than their antecedents, which are tertiary amines. Ipratropium, tiotropium, and aclidinium are structurally related to atropine, while oxitropium is a congener of scopolamine. Unlike the belladonna alkaloids, these drugs have minimal effects on mucociliary clearance of the airway and hence avoid the potentially dangerous reduction of airway secretions (and resultant inspissations of viscid material that lead to worsening obstruction and infection) seen with atropine and scopolamine. All of these agents are given via inhalation.[8,9]

Atrovent® HFA ([ipratropium HFA] Inhalation Aersol [Package Insert] Ridgefield, CT: Boehringer Ingelheim) is available in aerosol and nebulizer formulation. The recommended dosage is 36 mcg via metered-dose inhaler (MDI) (each MDI actuation delivers 18 mcg) or 500 mcg via nebulizer (2.5 ml of 0.02% solution), 4 times a day. Ipratropium alone or in combination with albuterol has been used extensively. Studies in the 1980s showed both an improvement in forced expiratory volume in 1 second (FEV_1) and reduction of hyperinflation with use of ipratropium.[10]

Oxitropium has a slightly longer duration of action than ipratropium and is used 2–3 times daily at a dose of 200 mcg (100 mcg/puff). It was marketed in an MDI form in Europe but was not made available commercially in the USA. This medication was discontinued in 2004. Oxitropium alone or in combination with an inhalational beta agonist has been shown to improve FEV_1 and exercise capacity.[11,12]

Tiotropium is available in a dry powder inhaler (DPI) and is used at a dose of 18 mcg daily. As it is predominantly renally excreted, patients with moderate to severe renal impairment (creatinine clearance $\leq$ 50 mL/min) who are on tiotropium should be monitored closely for evidence of anticholinergic side effects. Tiotropium has been studied extensively in many clinical trials. The trials showed that tiotropium improved lung function, reduced lung hyperinflation, improved exercise capacity, reduced COPD exacerbations, and improved quality of life.[13–15] In long-term studies, ipratropium and tiotropium did not reduce lung function decline.[6,13]

Aclidinium bromide is available in the form of DPI (with 60 doses per device) that delivers 400 mcg. Aclidinium has been found to improve peak and trough FEV_1, exercise capacity, and quality of life and to reduce the acute COPD exacerbations.[16]

Factors affecting safety of inhalational anticholinergics

Side effects are fairly similar for the four compounds. Dry mouth is the commonest adverse event observed with all agents. Other common adverse reactions include blurred vision, sore throat, rhinorrhea, constipation, and nausea.[10] In comparison with ipratropium and tiotropium, aclidinium was found to show less known anticholinergic effects, such as heart rate increase, urinary retention/difficulty, dry mouth, and constipation.[17] Some side effects, listed by the affected organ system, are given in the "safety profile of inhalational anticholinergics" section below.

Pharmacokinetic-related factors

The pharmacodynamic and pharmacokinetic characteristics of inhalational anticholinergics play an important role in the efficacy and safety profile of these agents. All the inhaled agents result in less systemic exposure compared with agents that are taken orally or intravenously. This leads to a wider therapeutic index and excellent tolerance profile for all the inhalational medications. All the currently available anticholinergics are water-soluble agents and hence have limited penetration across biological membranes. When given in the inhaled form, they have reduced systemic absorption and are

less likely to cross the blood–brain barrier. Table 1 provides the characteristics of inhaled anticholinergic agents currently approved for use in the treatment of COPD.[9]

Ipratropium is a short-acting anticholinergic that has been in use for decades. Between 10%–30% of inhaled ipratropium is deposited in the lungs and almost all of that is systemically bioavailable, while only 2% of the swallowed part may be absorbed systemically. The majority of the systemically absorbed ipratropium and its metabolites are excreted renally.[8]

Tiotropium is the first long-acting inhalational anticholinergic to be approved by the FDA for use in COPD. The systemically absorbed tiotropium is mainly eliminated by the urinary tract. Further, the renal clearance of tiotropium exceeds the creatinine clearance, which suggests the presence of active secretion into kidney tubules. Thus, renal impairment may affect its elimination and its safety profile.[8]

Aclidinium is metabolized rapidly by plasma esterases, resulting in a very low maximum plasma concentration and thus low systemic exposure. Aclidinium is eliminated as its metabolite in urine (close to two-thirds of a dose) and in feces (close to one-third of a dose). Renal and liver clearances play minor roles in the total clearance of aclidinium bromide from plasma and dose adjustment is not needed.[8,17] The residence time of aclidinium in the muscarinic acetylcholine M2 receptor is short and may explain the favorable cardiovascular profile.[17]

Device-related factors

With the increasing number of devices available, the type of delivery device and its effect on the dose delivered, and thus safety, should be considered. A particular case in point is the delivery of tiotropium by two different devices. Currently, the FDA has approved tiotropium in the form of DPI, when used with the Handihaler® (Boehringer Ingelheim Pharma GmbH and Co, KG, Ingelheim, Germany). In contrast, tiotropium also is manufactured to be delivered with a nebulizer device called the Respimat® (Boehringer Ingelheim Pharma). A recent meta-analysis showed an increased risk of death in COPD patients taking 5 micrograms of tiotropium by Respimat (recommended dose in Europe).[18] It is speculated that the Respimat may be delivering a higher concentration of tiotropium to the lungs, possibly resulting in a higher systemic concentration and side effects.[18] Thus, the delivery mechanism may play an important role in the safety profile of a medication. An ongoing large study is comparing effects of two different doses of tiotropium Respimat (1.25 and 2.5 mcg) and the approved dose of tiotropium Handihaler (18 mcg) on COPD exacerbations and mortality.[19]

Host-related (intrinsic) factors

The major issues related to the host revolve around the effects of age, sex, ethnicity, and disease severity on the efficacy and safety profile of the medications.

Aging is an important factor in the adverse effects of pharmaceutical agents. Elderly patients have less reserve, more comorbid conditions, and altered metabolism, and are most likely on multiple medications.[20] Any of these factors may predispose an elderly individual to adverse effects from inhalational anticholinergics. The efficacy and safety of a medication depends on many drug related and host related characteristics, including pharmacodynamics and pharmacokinetics of the agents. With aging, not only does organ function change, but also body fat distribution is altered.[21] The hepatic system in particular, and its ability to handle medications, changes significantly. Further, the presence of various comorbid conditions and polypharmacy are important contributing factors that can affect the response to medications.[20] Lastly, the elderly may differ genetically from middle-aged adults because of survivor bias.

Sex differences in drug metabolism may play a role in the efficacy and safety of medications, especially anesthetics,

Table 1 Characteristics of inhaled anticholinergic agents currently approved for use in the treatment of COPD

	Ipratropium bromide	Oxitropium bromide	Tiotropium bromide	Aclidinium bromide
Onset of action	15 min	15 min	30 min	15 min
Peak bronchodilation	1–2 hrs	60–90 min	3 hrs	2 hrs
Duration of action	3–6 hrs	5–8 hrs	24+ hrs	12 hrs
Usual dosage	MDI: 36 mcg (18 mcg/puff), 4 times/day Nebulizer dose: 500 mcg (200 mcg/mL), 4 times/day	MDI: 200 mcg (100 mcg/puff), 2–3 times/day	DPI: 18 mcg (1 capsule), 1 time/day	DPI: 400 mcg (375 mcg at mouthpiece), 2 times/day
Chief receptor antagonism	M1, M3 > M2	M1, M2, M3	M1, M3	M3, M1, M2

Note: Copyright © 2007, Daedalus Enterprises Inc. Adapted with permission from Restrepo RD. Use of inhaled anticholinergic agents in obstructive airway disease. *Respir Care*. 2007;52(1):833–851.[9]

Abbreviations: MDI, metered-dose inhaler; M, muscarinic acetylcholine receptor; DPI, dry powder inhaler.

HIV-1 therapies, and antiarrhythmic drugs.[22] In spontaneous reports to a local pharmacovigilance center, adverse drug reactions to respiratory medications were greater in females than in males.[23] In a report of the TRISTAN study, there was no difference between male and female participants in the efficacy and safety of the combination of an inhaled corticosteroid and a long-acting beta agonist.[24]

Race may play a role in the ability to metabolize medications.[25] However, data are limited on the effect of race on the metabolism of inhalational medications. The majority of patients enrolled in randomized clinical trials of COPD are Caucasian. However, some trials tried to either enroll minorities or compare the data among various ethnicities. Criner et al[26] conducted a randomized placebo-controlled trial of tiotropium delivered with the Handihaler in COPD patients of African American descent. The study did not show a different safety profile compared with other tiotropium trials. In a post hoc analysis of a large randomized clinical trial of tiotropium in COPD, Rice et al[27] did not report different safety profiles in the patients of African American descent compared with whites. A recent meta-analysis that included a randomized clinical trial in Chinese patients showed an efficacy and safety profile that was similar to that of whites.[28] Thus, the limited available data does not show different safety profiles for various ethnic groups.

Studies of tiotropium in asthmatics with varying severity of lung function impairment have shown some minor influence of disease severity on urinary excretion of the drug (decreasing excretion with increasing severity). However, the studies in COPD did not show any significant effects of disease severity, as measured by FEV_1, on urinary excretion.[29]

Safety profile of inhalational anticholinergics

Mortality

The safety of inhaled anticholinergics with regard to mortality has been a matter of debate. The Lung Health Study[30] morbidity and mortality results did not show differences in overall mortality between the ipratropium and placebo arms. However, cardiovascular death, in a pair-wise comparison (with no adjustment for multiple comparisons), was significantly higher in the ipratropium group compared with the placebo group; this significance disappeared when adjusting for multiple comparisons. In contrast, a pooled analysis of tiotropium pivotal data did not show any increase in mortality (all-cause or cardiovascular) compared with the placebo data.[31] However, a recent publication raised concerns about the safety of inhalational anticholinergics in regard to mortality and cardiovascular comorbidities. Singh et al,[32] in a meta-analysis of 17 randomized controlled trials (RCTs), reported an increased risk of major cardiovascular events (stroke, myocardial infarction, and cardiovascular deaths, including sudden death) with inhaled anticholinergics (relative risk 1.58; 95% confidence interval [CI], 1.21 to 2.06; $P < 0.001$). In contrast, in the longest and largest RCT of tiotropium to date (Understanding Potential Long-Term Impacts on Function with Tiotropium [UPLIFT]), with 17,721 patient-years of exposure, mortality did not differ significantly between the study arms (14.9% in the tiotropium group and 16.5% in the placebo group, with hazard ratio, 0.89; 95% CI, 0.79 to 1.02).[13] The FDA concluded that, because of the strength of the UPLIFT data and methodological limitations of the Singh meta-analysis, the current data do not support the proposed increased risk of mortality with use of the tiotropium Handihaler.[33]

The jury is still out on the safety of tiotropium delivered by the Respimat. A recent meta-analysis of five RCTs of tiotropium delivered by the Respimat device raised some concerns about the safety of the medication delivered by the Respimat. Singh et al[18] reported an increased mortality rate (90/3686 vs 47/2836; relative risk 1.52; 95% CI, 1.06 to 2.16; $P = 0.02$) with tiotropium Respimat compared with placebo. The higher peak plasma concentration of Respimat compared with Handihaler may play a role in the different safety profiles of the two delivery methods in regards to tiotropium.[18,34] A large RCT comparing tiotropium delivered by Respimat versus Handihaler is ongoing to assess the effect of tiotropium on mortality as well as other outcomes.[19]

The mortality data on aclidinium is much more limited. However, in pivotal registration studies the mortality did not differ among various doses and placebo.[17]

It is well known that clinical trials of COPD pharmacotherapy have extensive exclusion criteria. Thus, clinical trials may not be a comprehensive representation of all COPD patients that receive treatment with the approved agents. Investigators in the Lung Health Study noted that nine of the patients on ipratropium compared with two on placebo were hospitalized for supraventricular tachycardia. The nine on ipratropium were unusually compliant with their inhaled medication. Lee et al[35] analyzed Veterans Affairs administrative databases and found an increased adjusted odds ratio of all-cause mortality of 1.11 (CI, 1.08 to 1.15) for ipratropium. Further, ipratropium exposure was associated with a 34% increase in the odds of cardiovascular death (odds ratio [OR], 1.34 [CI, 1.22 to 1.47]). Thus, practitioners should exercise caution with use of inhalational anticholinergics and closely

monitor those patients at risk for cardiovascular disease and specifically, arrhythmias.

Cardiovascular

The cardiovascular adverse events related to inhalational anticholinergics include arrhythmias (including supraventricular tachycardia and atrial fibrillation), angina, nonspecific chest pain, and edema.

A study of administrative databases reported increased cardiovascular events associated with the use of ipratropium.[36] However, these findings were not substantiated in the RCTs of tiotropium. Pooled analysis of all the pivotal studies of tiotropium did not show an increased incidence of serious cardiovascular events. Similarly, the incidence of serious cardiac arrhythmias (including atrial fibrillation) was not higher in the tiotropium group.[31,37] Considering that UPLIFT followed the patients for much longer period of time, the review of the cardiovascular serious adverse events in the study is very informative. The incidence of serious cardiac events were significantly lower in the tiotropium arm compared with placebo (3.56 vs 4.21 with relative risk of 0.84 [CI, 0.73 to 0.98; $P < 0.05$]). Interestingly, the incidence of atrial fibrillation did not differ between the study arms. Further, incidences of congestive heart failure and myocardial infarction were numerically and statistically lower in the tiotropium compared with placebo arm.

Data on the safety profile of aclidinium is limited. In the data presented to FDA, the incidence of serious cardiovascular events was very low. Analysis of pivotal studies did not show an increase in cardiovascular events including arrhythmias. Similarly, the incidence of stroke was not higher with exposure to aclidinium.[17]

Respiratory

Respiratory adverse events reported with the use of inhalational anticholinergics include rhinitis, epistaxis, sinusitis, pharyngitis, laryngitis, throat irritation, cough, and upper respiratory tract infections.[38] In 0.3% of cases, acute paradoxical bronchospasm can be seen as an idiosyncratic reaction with anticholinergic use.[10] Patients who are highly allergic to milk proteins are advised to avoid using tiotropium DPI because of trace amounts of milk protein in the lactose filler (package insert).[39]

Other effects

Gastrointestinal

Gastrointestinal side effects are among the most frequently reported side effects, and include dry mouth, dysgeusia, stomatitis, abdominal pain, constipation, dyspepsia, nausea, vomiting, dysphagia, and paralytic ileus. Apart from dry mouth, these are all rare events.

Genitourinary

The most frequently reported genitourinary complications of inhaled anticholinergics are urinary difficulty, urinary retention, and urinary tract infection. Various studies, including a pooled analysis of pivotal data on tiotropium, showed an increased risk of urinary retention with tiotropium compared with placebo.[31,37,40] Thus, these medications should be used with caution in patients with prostatic hypertrophy or bladder outlet obstruction.

Ophthalmic

Various ophthalmic side effects have been reported with the use of inhalational anticholinergics. These include blurred vision, elevated intraocular pressure, acute or worsening narrow-angle glaucoma, and cataracts. Patients with preexisting narrow-angle glaucoma need to be monitored closely when started on these agents.

Another important ophthalmic consideration is the occurrence of acute anisocoria in patients with loose-fitting nebulizer masks (resulting from the unequal exposure of the eyes to the anticholinergic medication and subsequent development of unilateral mydriasis).[41,42] Inadvertent contamination of an eye with the MDI or DPI can also lead to anisocoria. With tiotropium, due to its long half-life, the duration of anisocoria can last more than 24 hours.[10] It is crucial that health care professionals be aware of this potential scenario during the use of these agents, to avoid the extensive work-up usually pursued for anisocoria (eg, neurological imaging, electroencephalogram, neurological consultation).

It should be kept in mind that, although all of the above side effects have been reported with inhaled anticholinergic medications, the percentage of the patient population experiencing adverse events is small. In fact, when compared with placebo, no statistically significant increased incidence of individual adverse events has been observed across several studies.

Conclusion

Inhalational anticholinergics have emerged as major players in the management of stable COPD patients. Because of their efficacy and safety profile, they are universally recommended by various COPD guidelines. Clinical trials have demonstrated improvements in expiratory flow, exercise capacity, and quality of life, and reduction in lung

hyperinflation and acute exacerbations of COPD, in patients using these medications. The safety profile of the agents has been well studied in randomized clinical trials. However, the external validity of these data, and the applicability to the nonclinical trial patient setting, is always an important point to consider. Thus, as a general rule, practitioners must consider drug- and host-related factors when choosing any of the agents. Consequently, a close follow-up for assessment of efficacy and monitoring of safety is needed when a COPD patient is started and maintained on these medications.

Disclosure

Dr Gross is an advisory board member and/or consultant for AstraZeneca, Boehringer-Ingelheim, Pfizer, Forest, Almirall, Elevation, Mylan Specialty, GSK, and Alexza; achieved grant support from Almirall, Forest, Boehringer, Dey LP, and Boehringer; and is on the speaking board for AstraZeneca, Forest, and Boehringer. Dr Sharafkhaneh is a member of the advisory board for Mylan. The authors report no other conflicts of interest in this work.

References

1. Miniño AM, Xu J, Kochanek KD. *Deaths: Preliminary Data for 2008*. Atlanta: Centers for Disease Control and Prevention; 2010. Available from: http://www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_02.pdf. Accessed August 30, 2012.
2. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance – United States, 1971–2000. *MMWR Surveill Summ*. 2002;51(6):1–16.
3. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176:532–555.
4. Cooper CB. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. *Am J Med*. 2006;119(10 Suppl 1):21–31.
5. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23(6):932–946.
6. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA*. 1994;272(19):1497–1505.
7. Rabe KF, Beghé B, Luppi F, Fabbri LM. Update in chronic obstructive pulmonary disease 2006. *Am J Respir Crit Care Med*. 2007;175(12):1222–1232.
8. Moulton BC, Fryer AD. Muscarinic receptor antagonists, from folklore to pharmacology; finding drugs that actually work in asthma and COPD. *Br J Pharmacol*. 2001;163(1):44–52.
9. Restrepo RD. Use of inhaled anticholinergic agents in obstructive airway disease. *Respir Care*. 2007;52(1):833–851.
10. Gross NJ. Anticholinergic agents in asthma and COPD. *Eur J Pharmacol*. 2006;533(1–3):36–39.
11. Oga T, Nishimura K, Tsukino M, Hajiro T, Ikeda A, Izumi T. The effects of oxitropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease. A comparison of three different exercise tests. *Am J Respir Crit Care Med*. 2000;161(6):1897–1901.
12. Cazzola M, Di Perna F, Califano C, Vinciguerra A, D'Amato M. Incremental benefit of adding oxitropium bromide to formoterol in patients with stable COPD. *Pulm Pharmacol Ther*. 1999;12(4):267–271.
13. Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543–1554.
14. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med*. 2005;143(5):317–326.
15. O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J*. 2004;23(6):832–840.
16. Sims MW, Panettieri RA Jr. Profile of aclidinium bromide in the treatment of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2011;6:457–466.
17. Food and Drug Administration (FDA), editor. NDA 202-450: aclidinium bromide for the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Paper presented at: Pulmonary Allergy Drugs Advisory Committee Meeting; 2012 Feb 23; Silver Spring, MD. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PulmonaryAllergyDrugsAdvisoryCommittee/UCM292620.pdf. Accessed August 30, 2012.
18. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2011;342:d3215.
19. Boehringer Ingelheim Pharmaceuticals. Comparison of tiotropium in the HandhiHaler versus the Respimat in chronic obstructive pulmonary disease. In: ClinicalTrials.gov [website on the Internet]. Bethesda, MD: US National Institutes of Health; 2011 [updated October 30, 2012]. Available from: http://clinicaltrials.gov/ct2/show/NCT01126437?term=tiotropium&rank=21. NLM identifier: NCT01126437. Accessed August 30, 2012.
20. McLachlan AJ, Pont LG. Drug metabolism in older people – a key consideration in achieving optimal outcomes with medicines. *J Gerontol A Biol Sci Med Sci*. 2012;67(2):175–180.
21. McLachlan AJ, Hilmer SN, Le Couteur DG. Variability in response to medicines in older people: phenotypic and genotypic factors. *Clin Pharmacol Ther*. 2009;85(4):431–433.
22. Nicolson TJ, Mellor HR, Roberts RR. Gender differences in drug toxicity. *Trends Pharmacol Sci*. 2010;31(3):108–114.
23. Montastruc JL, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. *Fundam Clin Pharmacol*. 2002;16(5):343–346.
24. Vestbo J, Soriano JB, Anderson JA, Calverley P, Pauwels R, Jones P; TRISTAN Study Group. Gender does not influence the response to the combination of salmeterol and fluticasone propionate in COPD. *Respir Med*. 2004;98(11):1045–1050.
25. Phan VH, Moore MM, McLachlan AJ, Piquette-Miller M, Xu H, Clarke SJ. Ethnic differences in drug metabolism and toxicity from chemotherapy. *Expert Opin Drug Metab Toxicol*. 2009;5(3):243–257.
26. Criner GJ, Sharafkhaneh A, Player R, et al. Efficacy of tiotropium inhalation powder in african-american patients with chronic obstructive pulmonary disease. *COPD*. 2008;5(1):35–41.
27. Rice KL, Leimer I, Kesten S, Niewoehner DE. Responses to tiotropium in African-American and Caucasian patients with chronic obstructive pulmonary disease. *Transl Res*. 2008;152(2):88–94.
28. Wu Q, Li G, Lei WI, Zhou X. The efficacy and safety of tiotropium in Chinese patients with stable chronic obstructive pulmonary disease: a meta-analysis. *Respirology*. 2009;14(5):666–674.
29. Boehringer Ingelheim Pharmaceutical. Spiriva Handihaler, 2001. http://www.fda.gov/ohrms/dockets/ac/02/briefing/3890b1_06_Pharmacology-Biopharmaceutics.pdf. Accessed August 30, 2012.

30. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med*. 2002;166(3):333–339.
31. Kesten S, Celli B, Decramer M, Leimer I, Tashkin D. Tiotropium HandiHaler in the treatment of COPD: a safety review. *Int J Chron Obstruct Pulmon Dis*. 2009;4:397–409.
32. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008;300(12):1439–1450.
33. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *N Engl J Med*. 2010;363(12):1097–1099.
34. van Noord JA, Cornelissen PJ, Aumann JL, Platz J, Mueller A, Fogarty C. The efficacy of tiotropium administered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. *Respir Med*. 2009;103(1):22–29.
35. Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med*. 2008;149(6):380–390.
36. Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular events associated with ipratropium bromide in COPD. *Chest*. 2010;137(1):13–19.
37. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest*. 2006;130(6):1695–1703.
38. Oba Y, Zaza T, Thameem DM. Safety, tolerability and risk benefit analysis of tiotropium in COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3(4):575–584.
39. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest*. 2006;130(6):1695–1703.
40. Spiriva Handihaler® Capsule (Tiotropium Bromide Inhalational Powder) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2004.
41. Lust K, Livingstone I. Nebulizer-induced anisocoria. *Ann Intern Med*. 1998;128(4):327.
42. Wehbe E, Antoun SA, Moussa J, Nassif I. Transient anisocoria caused by aerosolized ipratropium bromide exposure from an ill-fitting face mask. *J Neuroophthalmol*. 2008;28(3):236–237.