Title

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Publication Date

2015

DOI

10.2147/ppa.s71535

Peer reviewed

Patient Preference and Adherence

Dovepress
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Open Access Full Text Article

REVIEW

Patient considerations in the treatment of COPD: focus on the new combination inhaler umeclidinium/vilanterol

This article was published in the following Dove Press journal:
Patient Preference and Adherence
2 February 2015
Number of times this article has been viewed

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Abstract: Medication adherence among patients with chronic diseases, such as COPD, may be suboptimal, and many factors contribute to this poor adherence. One major factor is the frequency of medication dosing. Once-daily dosing has been shown to be an important variable in medication adherence in chronic diseases, such as COPD. New inhalers that only require once-daily dosing are becoming more widely available. Combination once-daily inhalers that combine any two of the following three agents are now available: 1) a long-acting muscarinic antagonist; 2) a long acting beta$_2$ agonist; and 3) an inhaled corticosteroid. A new once-daily inhaler with both a long-acting muscarinic antagonist, umeclidinium bromide, and a long acting beta$_2$ agonist, vilanterol trifenatate, is now available worldwide for COPD treatment. It provides COPD patients convenience, efficacy, and a very favorable adverse-effects profile. Additional once-daily combination inhalers are available or will soon be available for COPD patients worldwide. The use of once-daily combination inhalers will likely become the standard maintenance management approach in the treatment of COPD because they improve medication adherence.

Keywords: medication adherence, long-acting beta$_2$ agonist, long-acting muscarinic antagonist, inhaled corticosteroid, chronic obstructive pulmonary disease

Introduction

COPD is a syndrome that is a major and steadily increasing cause of chronic morbidity and mortality worldwide.[1] In a recent, large, Western European epidemiological study, the incidence rate of physician-diagnosed COPD was 2.92/1,000 persons–years and the prevalence was 3.02% (95% confidence interval [CI], 2.94%–3.10%).[1] The prevalence of COPD increases with age; it has been climbing globally since 1990 and is expected to continue to do so through 2020 as the population of current and former smokers ages.[2] COPD is underdiagnosed both in its early stages and when it is more advanced.[2] Reducing further lung exposure to cigarette smoke, which is the single most important causal factor in the development of COPD, will help reduce this substantial disease burden. However, not all COPD is related to smoking; other risk factors for the disease include genetic factors and other environmental and occupational exposures.[3]

Because of the huge health burden that COPD represents, new medications continue to be developed to treat the symptoms of COPD. This review will focus on adherence to the use of these medications with a particular focus on the once-a-day dry powder fixed-dose combination of umeclidinium bromide, a long-acting muscarinic

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antagonist (LAMA), and vilanterol trifenatate, a long-acting beta$_2$ agonist (LABA), for the treatment of COPD.

Effect of dosing frequency on medication adherence in chronic disease

The adherence to medication use in chronic disease is influenced by a number of factors. Individual factors such as socioeconomic status, age, sex, race, and mental status and health system factors such as health literacy, convenience of pharmacy, and the complexity of the medication regimens all contribute to medication adherence by chronically diseased patients.[4,5] Looking at patients with geriatric depression, human immunodeficiency virus, diabetes mellitus, and hypertension, Libby et al used the Medication Regimen Complexity Index to evaluate medication adherence. They found that dosing frequency and the variety of dosage forms were important components of medication complexity.[4] They recommended reducing complexity, such as decreasing dosing frequencies, for all chronic disease management programs.

The association of better dosing adherence with less frequent dosing has been reported in systematic reviews and meta-analyses performed for chronic psychiatric disease,[6] for chronic cardiovascular disease,[7,8] and for venous thromboembolism.[9] In a large, systematic review of dosing frequency and medication adherence in chronic disease, Coleman et al reported that the percentage values of adjusted weighted-mean–adherence rates compared to those for once-a-day dosing were 6.7% lower for two times-a-day, 13.5% lower for three times-a-day, and 19.2% lower for four times-a-day dosing regimens.[10] Timing adherence was even worse; compared to the rate for once-a-day dosing, the rates were 26.7% lower for twice-a-day dosing, 39.0% lower for three-times-a-day dosing, and 54.2% lower for four-times-a-day dosing.[10] Another systematic review of dosing-frequency adherence in chronic diseases found that patients were statistically ($P<0.05$) more compliant with once-a-day dosing regimens than with twice-daily or thrice-daily dosing regimens.[11] Dosing frequency clearly plays an important role in predicting medication adherence in chronic disease, and once-daily dosing regimens show the best adherence.

Medication adherence in COPD

Medication adherence in patients with COPD, like with all chronic diseases, is a complex issue, but adherence is crucial for the best outcomes. The addition of inhaled medications to an oral regimen further adds to this complexity. In a study of 575 Medicare beneficiaries in California, 70% reported taking medications "all of the time". Forgetfulness, side effects, difficulty paying for medications, complicated administration instructions, complicated drug names, and English as a second language were all identified as adherence barriers.[5] In COPD, poor inhaler technique has been associated with inadequate training and poor outcomes.[12,13]

Poor health-related quality of life (HRQOL) has also been associated with poor medication adherence in COPD. Other studies have suggested that an improved HRQOL in COPD can also trigger medication nonadherence.[14,15] This dual relationship between medication adherence and HRQOL suggests that the dynamics between the two can differ over time. In another study, no association between medication compliance and demographic variables was reported for COPD, but adherence was related to the classes of medication (eg, patients on steroids and antibiotics adhered more to their medication prescriptions than did those using theophylline or inhalers) and situational variables (eg, forgetting a dose related to feeling good, a change in routine, or the inconvenience of dosing).[16] There are limited amounts of data to support the roles that reduced out-of-pocket expenses, the use of case management, and patient education have in improving long-term medication adherence and health outcomes in a variety of disease states, as discussed in a recent systematic review.[17] In other studies, patient satisfaction with the inhaler, knowledge and education about the inhaler, inhaler convenience, and medication costs have been shown to be factors in medication adherence in COPD.[18,19] This benefit is often enhanced with the addition of pulmonary rehabilitation and group education programs.[17] Electronic medication delivery devices that give the COPD patient feedback and disease and medication education by pharmacists and the primary care team are advocated as ways to improve medication adherence in COPD, but again, the amount of quality data to support the recommendations is limited.[20–22]

In a retrospective study using a large administrative claims database and controlling for demographics, comorbidities, and baseline resources, medication adherence in 55,076 COPD patients strongly correlated with dosing frequency.[23] Adherence measured as the proportion of days in which prescribed drugs were used over 12 months was 43.7% for once-a-day, 37.0% for twice-a-day, 30.2% for three times-a-day, and 23.0% for four times-a-day dosing. Through the use of an administrative database of COPD patients and after controlling for potentially confounding factors, it was found that multiple-inhaler users experienced more exacerbations and had higher health care costs than did single-inhaler users.[24]

Combination-product inhalers have been advocated to improve medication adherence in the treatment of COPD for some time.[25] Several studies have suggested better adherence and outcomes when COPD patients use combination inhalers over single-product inhalers.[26–28] These studies are often confounded by comparing a combination steroid/bronchodilator inhaler to a single bronchodilator inhaler. In a systematic review of ten articles on medication adherence in COPD from 2008–2009, Charles found that the twice-a-day combination inhaler fluticasone propionate/salmeterol xinafoate combined with the once-a-day inhaler tiotropium was associated with the highest adherence among all controller medications available at that time.[21] Together, these data suggest that medication adherence by COPD patients is poor and that the reasons are multifactorial. Inhalers that use combinations of medications in conjunction with once-a-day dosing frequencies can improve medication adherence in these patients. Table 1 is a summary of current inhalers that are dosed once-a-day, and Table 2 offers the current combination drug inhalers that are available and approved by the US Food and Drug Administration (FDA).

Once-a-day, long-acting inhalers in COPD

The healthcare costs for patients with COPD increased by 38% between 1987 and 2007 in the USA and continued to increase by approximately 5% annually between 2006 and 2009.[29] The major driver for this increase was the cost of acute exacerbations of COPD; annual healthcare costs are tenfold greater for COPD patients with exacerbations than for those without. The use of LABAs, LAMAs, and ICSs as maintenance therapy remain underutilized; only 30%–35% of COPD patients receive prescriptions for maintenance therapy.[29]

In a systematic review, the use of twice-daily LABAs by patients with moderate-to-severe COPD was more effective over the medium term and long term than was the use of the placebo. Their use was associated with improved quality of life and reduced COPD exacerbations.[30] New once-daily LABA inhalers that have been approved by the FDA for use in COPD include olodaterol, delivered by the spring-driven mist (SDM) device Respimat®, and indacaterol, delivered as a dry powder.[31–34] In a systematic review of randomized, controlled clinical trials in patients with COPD, a similar efficacy with olodaterol and indacaterol was reported.[35]

The use of the inhaled LAMA tiotropium and the use of a placebo was compared in a systematic review. In the review, inhaled tiotropium treatment once-a-day was associated with significant improvement in the patient's quality of life and resulted in a reduction in the risk of exacerbations.[36] In another review of tiotropium bromide inhalation for COPD, it was also concluded that the once-daily LAMA was associated with improved lung function, dyspnea, and HRQOL scores, and was associated with the reduced incidence of acute COPD exacerbations.[37] By using claims data, inhaled tiotropium was found to be associated with a higher adherence than was twice-daily inhaled fluticasone/salmeterol among COPD patients. Medication adherence in this study was associated with lower respiratory-related medical and inpatient costs.[38] Another retrospective study in the USA reported fewer COPD exacerbations, hospitalizations, and hospital days among patients receiving tiotropium. This resulted in a reduction of total healthcare costs of greater than $1,000 per patient in the tiotropium-treated group.[39]

The dry powder, once-daily combination inhaler with the LABA vilanterol and the ICS fluticasone furoate has been approved by the FDA for the treatment of COPD. Significant improvement in lung function was demonstrated in moderate-to-severe COPD patients using that therapy.[40–42] In addition, once-daily inhalation of fluticasone furoate and vilanterol was associated with a decrease in moderate and severe COPD exacerbations in patients with a history of exacerbations. This reduction in exacerbations was also associated with a small increase in the risk of pneumonia.[43]

Table 1 Once a day inhalers used in COPD

Drug(s)	Dose per inhalation	Drug type	Inhaler type	Brand name
Umeclidinium bromide + vilanterol trifenatate	0.0625 mg +0.025 mg	LAMA + LABA	Dry powder	Anoro Ellipta®,C
Fluticasone furoate + vilanterol trifenatate	0.1 mg +0.025 mg	ICS + LABA	Dry powder	Breo Ellipta®,C
Indacaterol maleate	0.075 mg	LABA	Dry powder	Arcapta Neohaler®,C
Olodaterol hydrochloride	0.0025 mg[D]	LABA	SDM	Striverdi Respimat®,C
Tiotropium bromide	0.018 mg	LAMA	Dry powder	Spiriva Handihaler®,C
Tiotropium bromide	0.0025 mg[D]	LAMA	SDM	Spiriva Respimat®,C

Notes: [C]indicates an FDA approved indication for COPD; [D]indicates two inhalations of 0.0025 mg once daily.
Abbreviations: LAMA, long-acting muscarinic antagonist; LABA, long-acting beta$_2$ adrenergic agonist; ICS, inhaled corticosteroid; SDM, spring-driven mist inhaler; FDA, US Food and Drug Administration.

Table 2 Combination inhaled drugs for airway diseases

Drug combination	Dose per inhalation	Drug type	Frequency	Inhaler type	Brand name
Umeclidinium bromide + vilanterol trifenatate	0.0625 mg +0.025 mg	LAMA + LABA	qd	Dry powder	Anoro Ellipta®,C
Fluticasone furoate + vilanterol trifenatate	0.1 mg +0.025 mg	ICS + LABA	qd	Dry powder	Breo Ellipta®,C
Budesonide + Formoterol fumarate	0.08 mg +0.0045 mg or 0.16 mg +0.0045 mg	ICS + LABA	bid	MDI	Symbicort®,A,C
Fluticasone propionate + salmeterol xinafoate	0.1 mg +0.05 mg; 0.25 mg +0.05 mg; or 0.5 mg +0.05 mg	ICS + LABA	bid	Dry powder	Advair Diskus®,A,C
Fluticasone propionate + salmeterol xinafoate	0.045 mg +0.021 mg; 0.115 mg +0.021 mg; or 0.230 mg +0.021 mg	ICS + LABA	bid	MDI	Advair HFA®,A
Mometasone furoate + formoterol fumarate	0.1 mg +0.005 mg or 0.2 mg +0.005 mg	ICS + LABA	bid	MDI	Dulera®,A
Albuterol sulfate + ipratropium bromide	2.5 mg +0.5 mg	SABA + SAMA	qid	Neb	DuoNeb®,C + generics C
Albuterol sulfate + ipratropium bromide	0.1 mg +0.03 mg	SABA + SAMA	qid	SDM	Combivent Respimat®,C

Notes: [C]indicates an FDA approved indication for COPD; [A]indicates an FDA approved indication for asthma.
Abbreviations: LAMA, long-acting muscarinic antagonist; LABA, long-acting beta$_2$ agonist; ICS, inhaled corticosteroid; SABA, short-acting beta$_2$ agonist; SAMA, short-acting muscarinic antagonist; qd, once-a-day; bid, twice-a-day; qid, four times-a-day; MDI, metered dose inhaler; Neb, nebulized drug; SDM, spring-driven mist; FDA, US Food and Drug Administration.

Umeclidinium bromide is a new quinuclidine-based quaternary ammonium LAMA not yet FDA approved for use in COPD as a single agent. In a double-blind, placebo-controlled trial, once-daily inhalation of a dry powder of umeclidinium was compared to twice-daily doses and to once-daily tiotropium inhalation. Once-daily inhaled umeclidinium was associated with increases in lung function comparable to those seen with twice-daily dosing and with once-daily tiotropium, and all three were superior to the placebo.[44] Similar sustained improvement in lung function and a reduced need for short-acting beta$_2$ agonists (SABAs) have been reported with once-daily inhaled umeclidinium.[45,46]

The first long-acting combination inhaled bronchodilator was the LABA indacaterol paired with the LAMA glycopyrronium. It is approved in Japan, Europe, and Great Britain for maintenance therapy in COPD, but this combination has not been approved in the USA. In patients with moderate-to-severe COPD, once-daily inhaled indacaterol/glycopyrronium was associated with better improvement in forced expiratory volume 1-second (FEV_1) at week 12 than was a combination of indacaterol and a placebo.[47] The combination once-daily inhaler glycopyrronium/indacaterol was studied for 26 weeks in 2,144 moderate-to-severe COPD patients in the SHINE study.[48] The study researchers found greater improvement in trough FEV_1, dyspnea scores, and health status scores with this inhaler than with the inhaled placebo, indacaterol alone, glycopyrronium alone, or tiotropium alone.[48] In an analysis of a combination of five clinical trials (41,842 COPD patients), glycopyrronium alone, tiotropium alone, and a glycopyrronium/indacaterol combination were compared in a systematic review.[49] The once-daily combination inhaler was found to be associated with better trough FEV_1 (70 mL, $P<0.0001$) and less frequent use of rescue SABA inhalers (–0.63 puffs/day, $P<0.0001$) than was the once-daily LAMA tiotropium alone. The efficacy of glycopyrronium/indacaterol was shown to be superior to glycopyrronium inhaled alone in patients with moderate-to-severe COPD.[49]

In a study in Sweden, researchers evaluated the cost-effectiveness of indacaterol/glycopyrronium as a once-daily fixed-dose combination therapy in COPD patients and compared it to that of an indacaterol inhaler plus a glycopyrronium inhaler and to the fixed twice-daily inhaler salmeterol/fluticasone; they used data from the SHINE study and a cost-minimization analysis in which equal efficacy was assumed. After including direct and indirect drug acquisition costs in Sweden, the combination inhaler indacaterol/glycopyrronium was significantly cheaper than indacaterol inhaler plus glycopyrronium inhaler or the combined salmeterol/fluticasone inhaler.[50] Local indirect and direct drug costs can change these calculations, but in general combination inhalers are less expensive than the component drugs as individual inhalers.

The once-daily combination inhaler umeclidinium bromide/vilanterol trifenatate in the treatment of COPD

Currently, there are three fixed-dose combination long-acting once-daily inhalers approved in Europe and Japan for the

chronic treatment of COPD: the LAMA/LABA combination glycopyrronium/indacaterol, the ICS/LABA combination fluticasone/vilanterol, and the LAMA/LABA combination umeclidinium/vilanterol.[51] Two of these agents, fluticasone/vilanterol and umeclidinium/vilanterol, are currently FDA approved in the USA for treatment of COPD. The LAMA umeclidinium (62.5 µg) combined with the LABA vilanterol (25 µg) is approved for once-daily maintenance therapy of COPD in the USA.[52] When the umeclidinium/vilanterol (UMEC/VI) combined once-daily inhaler was compared to either an inhaler of umeclidinium alone, vilanterol alone, or placebo in 1,493 COPD patients over 24 weeks, greater improvements in lung function, health status, and dyspnea were seen with UMEC/VI than with the monotherapies or the placebo.[53] When the UMEC/VI inhaler was compared to the placebo inhaler, the hazard ratio for COPD exacerbation was 0.4 (95% CI, 0.2–0.6, $P \leq 0.001$), and rescue SABA albuterol (SABA) use decreased by 0.7 puffs/day for placebo and decreased by 2.2 puffs/day for UMEC/VI (difference of −1.7 puffs/day, $P \leq 0.001$) from week 1 to week 24.[53] In a double-blind, multicentered, double-dummy, parallel-group trial in 2,332 COPD patients treated for 24 weeks with high-dose (125 µg) UMEC/VI, low-dose (62.5 µg) UMEC/VI, VI (27 µg) alone, tiotropium alone, or high-dose UMEC alone, both doses of UMEC combined with VI were associated with better trough FEV_1 than was VI monotherapy. An improvement of 0.088 L (0.036–1.4 L, $P=0.001$) was seen for the 125 µg (high-dose) UMEC/VI regimen and 0.09 L improvement (0.039–0.142 L, $P=0.0006$) was seen for the 62.5 µg (low-dose) UMEC/VI regimen compared to VI alone.[54] No significant differences in symptoms, health status, or risk of exacerbation were seen between either of the two doses of combination UMEC/VI inhaler and either the tiotropium inhaler or the high-dose UMEC inhaler alone. For both doses of the UMEC/VI inhaler, trough FEV_1 values on day 169 were better than on day 1, and the improvement was more than was seen with the tiotropium inhaler alone. The difference between tiotropium and 125 µg (high-dose) UMEC/VI was 0.088 L (95% CI, 0.036–0.140, $P=0.001$); the difference between tiotropium and 62.5 µg (low-dose) UMEC/VI was 0.09 L (95% CI, 0.039–0.141 L, $P=0.006$).[54] The low dose UMEC (62.5 µg)/IV (25 µg) is the approved formulation in the USA. In a 24-week, double-blind, placebo-controlled trial of 1,532 COPD patients randomized to either UMEC (62.5 µg)/VI (25 µg), UMEC (62.5 µg) alone, VI (25 µg) alone, or placebo once-daily inhalers, lung-function indicators including trough FEV_1, symptoms, and HRQOL were assessed. All active treatments were associated with significantly greater trough FEV_1 than was the placebo (0.072–0.167 L, all $P<0.001$), and both combination UMEC/VI inhalers were significantly better than either monotherapy (0.052–0.095 L, $P \leq 0.004$).[55] Reduced use of the SABA albuterol rescue inhaler, better symptom scores, and improved HRQOL endpoints were also seen in a comparison of UMEC/VI with the placebo.

In safety and tolerability studies of high-dose UMEC (125–500 µg)/VI (25 µg) inhalers for COPD, patients who used the inhalers showed no differences in pulse rates, blood pressure, or corrected QT (QTc) intervals from the patients who took the placebo.[56,57] Over a 52 week trial, the incidence of ectopic supraventricular beats, sustained supraventricular tachycardia, and ectopic supraventricular rhythm were ≥2% with the high-dose (125 µg) UMEC/VI inhaler than with the placebo inhaler.[57]

There are no apparent pharmacokinetic interactions between umeclidinium and vilanterol when coadministered in patients with COPD.[58] When umeclidinium (500 µg) was combined with vilanterol (50 µg) by inhalation in healthy Japanese subjects, it was well tolerated. Both drugs showed rapid absorption with maximum serum concentrations within 5 minutes and with rapid elimination terminal half-lives of 0.42 hours for vilanterol and 0.71 hours for umeclidinium.[59] The maximal plasma concentration of umeclidinium was 995.9 pg/mL (776.0–1,278.1 pg/mL) and was 1,299.0 pg/mL (1,026.0–1,644.7 pg/mL) for vilanterol. The average heart rate increase was 4.8 (0.6–9.1) beats/minute.[59] In a large study of patients with COPD treated with fixed-dose umeclidinium and vilanterol inhalation, the pharmacokinetics was best described by a two-compartment model with first-order absorption. Again there was no apparent pharmacokinetic interaction when umeclidinium and vilanterol were coadministered in patients with COPD. Age, bodyweight, and creatinine clearance did not significantly affect systemic exposure to either drug after inhalation.[58] After inhalation of 125 µg umeclidinium and 25 µg vilanterol, the plasma concentration-time curves for umeclidinium and vilanterol were not significantly different between subjects with moderate hepatic impairment and healthy volunteers.[60]

In exploring potential cardiac effects, healthy nonsmokers received inhalers of UMEC 500 µg/VI 100 µg, UMEC 125 µg/VI 25 µg, UMEC 500 µg, or placebo for 10 days.[61] Following the 10-day treatment, no clinically significant differences in QTc intervals were observed between those who inhaled UMEC 500 µg/VI 100 µg, those who inhaled UMEC 125 µg/VI 25 µg, and those who took the placebo. The supratherapeutic dose of 500 µg of umeclidinium with the supratherapeutic dose of 100 µg of vilanterol by inhalation increased the QTc interval by 4.2–8.2 msec

from 5 to 30 minutes after dosing.[61] These changes were the same magnitude as the QTc interval changes seen with oral moxifloxacin (4.8–9.7 msec) 30 minutes to 12 hours after dosing.

Because these agents are very poorly absorbed, they are well tolerated. Antimuscarinic inhaled compounds have been associated with dry mouth, constipation, dyspepsia, gastroesophageal reflux, urinary retention, pupillary dilation, blurred vision, paradoxical bronchoconstriction, and worsening of glaucoma.[62] The adverse effects of LABA agents include palpitations, increased heart rates, supraventricular tachycardias, ectopy, nervousness, tremor, anxiety, hypokalemia, glycogenolysis, hyperglycemia, and paradoxical bronchoconstriction.[62] Drug-related adverse events reported with inhaled umeclidinium/vilanterol in clinical trials occurred at the rate of ≥1% and included headaches, nasopharyngitis, upper respiratory tract infections, dry mouth, dyspnea, and cough.[53,55]

Conclusion

Medication adherence is not optimal in patients with chronic diseases, such as COPD. Many factors contribute to this poor medication adherence. Medication dosing frequency is one of the variables that contributes to poor medication adherence in chronic diseases. Once-daily inhalers and particularly combination once-daily inhalers have been shown to improve medication adherence in COPD and are becoming more widely available as new products emerge on the market. The once-daily combination umeclidinium (LAMA)/vilanterol (LABA) inhaler meets the criteria for the treatment of COPD and has favorable efficacy and favorable adverse effects profiles. Because the specific data for the UMEC/VI combined inhaler are limited, improved adherence has not been studied, but this inhaler should theoretically improve medication compliance in COPD. Other once-daily LAMA/LABA combination inhalers are available, are under clinical trials, and are likely soon to be on the USA market. These once-daily combination inhalers will likely become standard maintenance therapy for patients with moderate-to-severe COPD.

Disclosure

TEA reports receiving speaking honorarium from BI and GSK to speak on COPD. The other authors report no conflicts of interest in this work.

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