SYSTEMATIC REVIEW

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Editor's Choice

Potential negative consequences of non-consented switch of inhaled medications and devices in asthma patients

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SUMMARY

Background: Asthma requires individually tailored and careful management to control and prevent symptoms and exacerbations. Selection of the most appropriate treatment is dependent on both the choice of drugs and inhaler device; however, financial pressures may result in patients being switched to alternative medications and devices in an attempt to reduce costs. **Aim:** This review aimed to examine the published literature in order to ascertain whether switching a patient's asthma medications or device negatively impacts clinical and economic outcomes. **Materials and methods:** A literature search of MEDLINE (2001–13 September 2011) was conducted to identify English-language articles focused on the direct impact of switching medications and inhaler devices and switching from fixed-dose combination to monocomponent therapy via separate inhalers in patients with asthma; the indirect impacts of switching were also assessed. **Results:** Evidence showed that non-consented switching of medications and inhalers in patients with asthma can be associated with a range of negative outcomes, at both individual and organisational levels. Factors that reduce adherence may lead to compromised symptom control resulting in increased healthcare resource utilisation and poorer patient quality of life. **Discussion:** The consequences of a non-consented switch should be weighed carefully against arguments supporting an inhaler switch without the patient's consent for non-medical/budgetary reasons, such as potential reductions in initial acquisition costs, which may be associated with subsequent additional healthcare needs. **Conclusion:** Given the increasing pressure for reduced costs and efficient allocation of limited healthcare resources, an additional investment in ensuring high medication adherence may lead to greater savings due to a potentially decreased demand for healthcare services. In contrast, savings achieved in acquisition costs may result in a greater net loss due to increased healthcare consumption caused by decreased asthma control.

Review criteria

A literature search of the MEDLINE database was conducted to identify English-language articles with content specific to the direct impact of switching medications and inhaler devices and switching from fixed-dose combination to monocomponent therapy via separate inhalers in patients with asthma; the indirect impacts of switching were also assessed. Conference abstracts were not included.

Message for the clinic

Switching medications and inhaler devices in patients with asthma without their consent or a medical need can result in increased demand for healthcare services. Prescribers should, therefore, not only consider the acquisition costs that may be potentially reduced by switching patients to lower cost products but also the potential subsequent costs of additional healthcare needs.

Introduction

Asthma is a complex disease requiring careful and individually tailored treatment (1). The main management goal is to control and prevent symptoms and exacerbations to achieve optimal lung function and quality of life (2). Selection of the most appropriate treatment regimen is dependent on both the choice of drugs and inhaler device (3). This should be a collaborative process between the physician and patient as the behaviour of both is an important determinant of the level of asthma control achieved (4). Once an effective treatment strategy has been found, it is feasible that the patient may remain on that regimen for many years (5). However, as asthma is a common condition associated with a considerable burden on healthcare budgets, there is always pressure for cost reductions (6–8). Switching a patient from one product to another should be performed to improve the management of symptoms, and increase patient compliance and convenience. Nevertheless, when financial issues arise, a likely strategy could be to switch well-controlled patients without their consent to potentially reduce treatment costs.

There are a large variety of inhaler devices available, and differences in design, handling technique, durability (i.e. shelf-life) and price between branded

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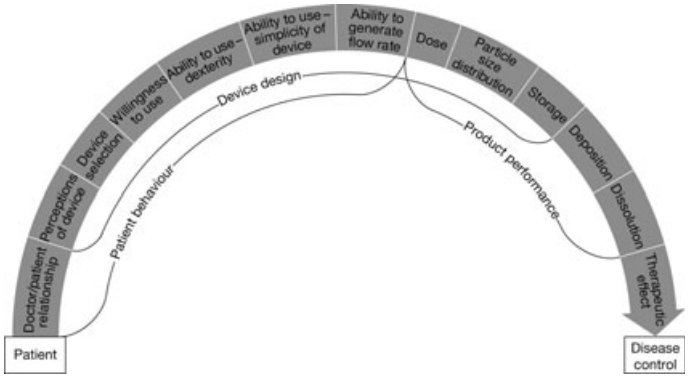

Figure 1 Stages between use of an inhaler by the patient and the therapeutic effect. Figure adapted from Price (7)

and analogue products can be great. Successful management of asthma symptoms is dependent on a number of factors (Figure 1). One key factor is correct inhaler use (9–11). Patients are more likely to achieve better asthma control as a result of successful dose delivery when they become familiar with a particular device. In the case of switching, it is crucial that the reason for the switch has been properly explained to the patient and instructions for operating the device correctly have been clearly demonstrated (5). Unfortunately, this does not always occur and reports of asthma patients having their medications switched without their consent (non-consented switch) have emerged (5).

Non-consented switching means that patients do not receive any counselling from their healthcare provider about the new medication and device, which may result in poor inhalation technique. This can negatively impact adherence and asthma control, and evidence suggests that treating asthma medications as interchangeable on an interclass basis can have detrimental effects on patient outcomes (5,7,12). It is therefore possible that switching may not result in cost savings, because of increases in clinic visits for education and support and negative impacts on asthma control, resulting in higher short- and long-term healthcare costs.

Objective

The objective of this review, which primarily focused on dry powder inhalers (DPIs), was to review the published literature to obtain a clearer picture regarding whether switching a patient's asthma medications or device negatively impacts clinical and economic outcomes.

Methods

Data were derived from published English-language papers listed in MEDLINE, and accessed via PubMed according to defined search terms. Searches were limited to full publications only; conference abstracts were not included. Only articles published between 2001 and 13 September 2011 were included. Three different searches were performed using keywords to identify publications that focused on:

- Monocomponents vs. fixed-dose combination (FDC) therapy: searches combined the terms bronchodilator and inhaled corticosteroids (ICS), asthma, single inhaler and combination inhaler.
- Consequences of switching devices: searches combined the terms bronchodilator and ICS, asthma, FDC or free-combination therapy, switching, device or inhaler (single inhaler or separate inhalers), adherence or compliance, asthma or symptom control and healthcare utilisation or costs.
- Adherence, cost-effectiveness and quality of life: searches combined the terms bronchodilator agents or ICS or glucocorticoid, adherence or compliance, cost-effectiveness or cost or health economics, quality of life, device or inhaler, training or technique or education or instruction, fixed or combination therapy or single inhaler therapy or separate inhaler or FDC or free combination or monotherapy or monocomponents and asthma. Resource use and resource utilisation were not included as search terms. This search was also limited to articles published between 2001 and 13 September 2011.

Abstracts of the articles identified via the three searches were analysed for content specific to the following topics:

- Direct impact of switching, including switching from combination therapy to monotherapy
  - Pharmaceutical performance
  - Inhalation technique
  - Adherence
  - Asthma control
- Indirect impact of switching
  - Healthcare resource consumption and costs.

Results

Direct impact of switching

The direct impact of switching has implications for pharmaceutical performance, inhalation technique and adherence, all factors that ultimately affect asthma control and quality of life (3,13).

Pharmaceutical performance

Currently, there are a large number of DPIs available; these devices differ greatly in their design and features (14). The effectiveness of devices with regard to the delivery of inhaled medications is dependent on many factors, such as design characteristics, medication, carrier, particle size, shape and density, lung deposition and ease of use (9). The increase in supply of DPIs has not correlated with a growth in knowledge of the disparity between products in terms of lung deposition and dose-delivery capabilities; there appears to be a prevailing assumption that devices are interchangeable and deliver the same dose of medication regardless of the inhaler (14). Differences between dose-delivery capabilities of DPIs have been explored in several studies, demonstrating that the pharmaceutical performance of different devices delivering the same molecule can vary widely, which has a great impact on asthma outcomes. Devices should, therefore, not be considered to be interchangeable with regard to pharmaceutical performance (12).

Inhalation technique

Dry powder inhalers also differ with respect to inhalation technique. Correct technique is critical for delivering the correct drug dose to the airways, and patient education is crucial (9,15). Each device requires a certain level of inhalation flow to ensure efficient disaggregation of the formulation; this may be problematic, for example, in children and the elderly, who may unable to produce the required inhalation flow, resulting in medication underuse.

Successful switching requires instruction on the correct inhaler technique and regular monitoring; incorrect use of a device is one of the most frequent concerns patients express after switching (9,14,16,17). To prevent confusion regarding techniques and the introduction of critical handling errors (i.e. those that result in little or no delivery of medication to the lungs), different types of inhalers should not be mixed for an individual patient (9,12,18,19).

When a patient follows an instruction leaflet, the first attempt to use a new device is often unsuccessful with a high probability of handling errors (15). This indicates that patients find it hard to understand written instructions on inhalation technique and need assistance and careful monitoring by a healthcare specialist. Reduced health literacy levels have been associated with poorer adherence in patients with respiratory diseases, and can be particularly relevant to certain subgroups of patients, for example, elderly people who may have difficulty reading (20). Elderly patients may also have problems recalling the correct technique, even if it has been demonstrated by a healthcare professional. In addition, depression has been identified as a risk factor for non-adherence, and such patients may be particularly sensitive to switching (21). The need for additional physician visits was underlined by Schulte et al. who noted that patients were better at handling the device after listening to instructions from a physician than after independently reading a leaflet (15). Indeed, in a recent cross-sectional observational study, lack of instruction on correct inhaler technique was the only modifiable factor significantly associated with critical handling errors (22).

Adherence

Adherence to treatment is essential for optimal asthma control; however, studies indicate that patients are poorly adherent and generally underuse their asthma medications (13,17,23). Decreased adherence, whether intentional or unintentional, is a common outcome of switching (17). Unintentional non-adherence may occur because of individual constraints, such as poor handling technique, critical handling errors, an inability to recall consultations, or environmental constraints, such as costs or difficulties accessing prescriptions. Intentional non-adherence may arise if a patient has a perception of asthma or a particular belief making them disinclined to adhere to treatment; for example, concerns regarding ICS or if a patient has low motivation to use an inhaler that is not their device of choice (4,15,24).

It is important that prescribers consider patient needs and preferences when choosing the most appropriate treatment choice as these factors contribute greatly to adherence (25,26). The choice is highly dependent on individual patient- and device-related factors such as availability of the drug and dose in the specific device, ability to develop and maintain an effective technique, suitability of the device, the fit of the regimen to the person's lifestyle, preference for and willingness to use a particular device, and patient confidence in the safety and efficacy of the treatment (25–27). These stages between inhaler use and therapeutic effect are outlined in Figure 1.

Adherence is also dependent on several non-drug- or -device-related factors, including patient–physician partnership and level of patient satisfaction with their device (25,26). Patients do not have equal preference for different DPIs (15), and for the majority

of patients, the higher the level of device satisfaction, the greater the likelihood of adherence leading to better outcomes (25).

Few studies have directly assessed adherence to FDCs of ICS/long-acting β_2-agonists (LABA) compared with ICS plus LABA administered via separate inhalers, as a true double-dummy technique is not possible. However, data from an open-label, randomised study and two retrospective observational analyses show that adherence tends to be higher with FDCs administered via a single inhaler rather than monocomponents via separate inhalers (28–30). Data also suggest that the minor benefits in certain patient-reported outcomes associated with FDCs (31), as well as fewer withdrawals from treatment and fewer prescriptions for other asthma medications, may be the result of single-inhaler therapy being more convenient than separate inhalers (32–34). In a real-world setting, this is likely to translate into greater patient adherence (32).

The consequences of a non-consented inhaler switch were assessed qualitatively by Doyle et al. via semi-structured face-to-face interviews with patients ($n = 19$) (5). Patients described struggling to actuate the new device, overuse of medication (especially rescue medication), feeling disempowered and a lack of personal control over their medical condition, damaging the relationship with their doctor as a consequence. The study concluded that the negative impact of switching must be seriously considered.

Important themes associated with interchangeability of DPIs were identified in a survey of asthma patients or parents of children aged 5–14 years with asthma ($n = 499$) from Australia, Canada, France, Germany and the UK using a Delphi process (35). Here, the majority (83%) of patients would raise concerns and questions regarding the switch, while one-half (51%) would oppose switching. The majority of patients (61%) also thought that it would be confusing to have their device changed, while 23% would ask for more information about the change or training regarding the new device.

Asthma control

Reduced medication adherence is directly related to reduced asthma control (36–38), resulting in an increased frequency of exacerbations (37,38) and asthma-related mortality (39). Retrospective analysis of a managed-care database examined the association between adherence and exacerbations in asthmatic patients with prescriptions for controller medications ($n = 97{,}743$) (38). More adherent patients were significantly less likely to experience exacerbations than less adherent patients. For all adherence cut-off points (≥ 2 through ≥ 6 prescriptions), there were significantly fewer exacerbations in more adherent than less adherent patients after adjusting for covariates. As the criteria for adherence became more stringent, more adherent patients became increasingly less likely to have an exacerbation than less adherent patients. Similarly, adherence to ICS has been shown to be significantly and negatively correlated with the number of emergency department visits, number of prescription fills of an OCS and total days of OCS use (37).

The increased probability of handling errors resulting from unfamiliar inhalation techniques may also result in reduced asthma control as a result of underdosing (9,16,22). The causal relationship between switching and lower asthma control was assessed by Thomas and Williams (40). Patients who were switched without being consulted by a physician had worse asthma control than those who stayed on the same treatment. The switched cohort were also more likely to use SABA, a marker for decreased asthma control, using 0.38 extra doses per day of SABA compared with the control group ($p < 0.001$). After adjusting for baseline confounding factors, the overall likelihood of unsuccessful treatment among the switched cohort was substantially higher than for those who stayed on the same medications (odds ratio: 1.92; 95% confidence interval: 1.47, 2.56; $p < 0.001$).

The causal relationship between poor device handling and poor asthma control has been investigated in two studies (22,36). In the study conducted by Molimard and Le Gros (36), the Asthma Control Score (ACS; where entirely controlled asthma was indexed by 0 and uncontrolled by 9) was calculated from data recorded in routine consultations of 4362 patients with persistent asthma using maintenance ICS-only treatment and correlated with patient characteristics, compliance (using two methods), and critical inhaler handling errors. More than 20% of patients were using their inhalers incorrectly, which was associated with a 0.84-point increase in the ACS. ACS was substantially better in patients who missed ≤ 4 doses per week than in those who were poorly compliant (missed > 4 doses per week). Asthma control was inadequate in 63% of those who missed > 4 doses per week compared with 38% of those who missed ≤ 4 doses per week. Similarly, Melani et al. investigated the relationship between inhaler device handling and disease control in 1664 adults, 42% of whom had asthma. Inhaler misuse was associated with an increased risk of poor disease control as measured by the Asthma Control Test ($p < 0.001$) (22).

Non-adherence leads to numerous adverse events associated with uncontrolled asthma (37), which, in turn, result in increased demand for healthcare resource (8). Therefore, it is necessary to emphasise

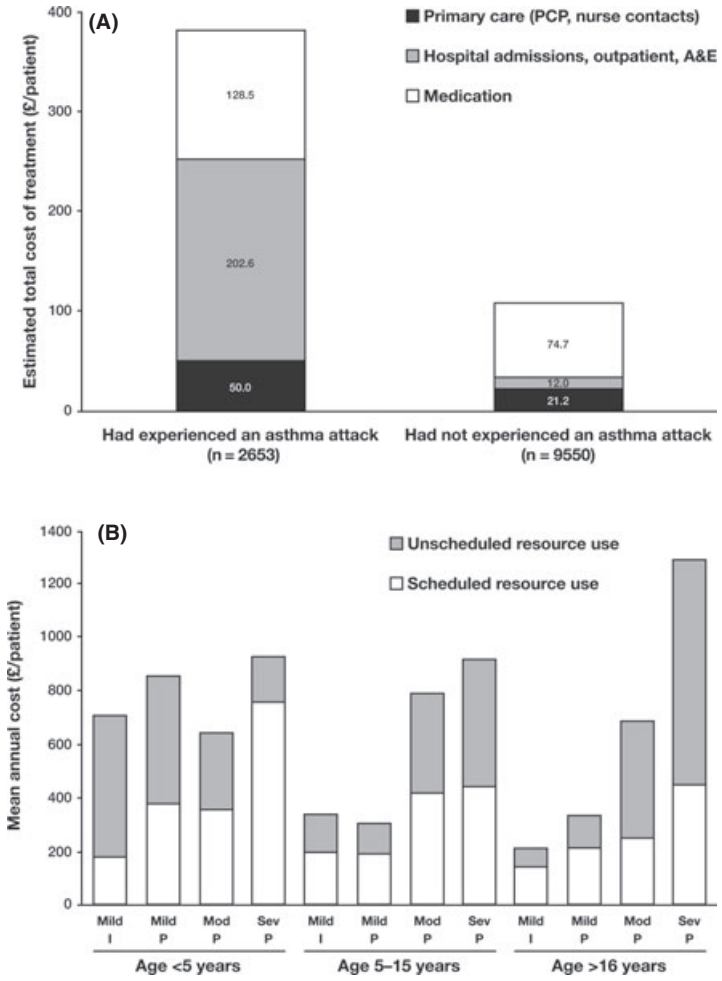

Figure 2 Costs of managing asthma patients: (A) with or without asthma exacerbations (published data on unit costs were used to assess the cost pattern of healthcare for each patient) (42), figure adapted from Price (7); and (B) with scheduled and unscheduled asthma healthcare visits by symptom severity and age group, figure adapted from Williams et al. (44). A&E, accidence and emergency; I, intermittent; Mod, moderate; P, persistent; PCP, primary care physician; Sev, severe

the importance of weighing the possible cost of adverse events against acquisition cost savings before initiating mass switching.

Indirect impact of switching

Healthcare resource consumption and costs

Non-consented switching and switching for non-medical reasons can have direct negative effects on disease control, resulting in increased healthcare resource consumption and costs (8). Indeed, poorly controlled asthma accounts for almost 50% of the total asthma healthcare burden (41). Annual treatment costs incurred by patients who have an exacerbation are three times higher than in those who do not (Figure 2A) (42). In addition, costs of asthma exacerbations in secondary care increase with increasing severity of exacerbations (43).

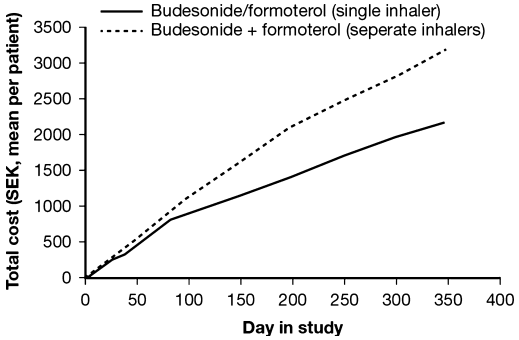

Figure 3 Change in direct and indirect total costs of fixed-dose budesonide/formoterol therapy vs. monocomponent therapy (1999 cost year) in patients with asthma, excluding study medication costs, over time; figure reproduced from Rosenhall et al. (33). As of April 2013: 1 SEK = 0.10 GBP = 0.53 USD

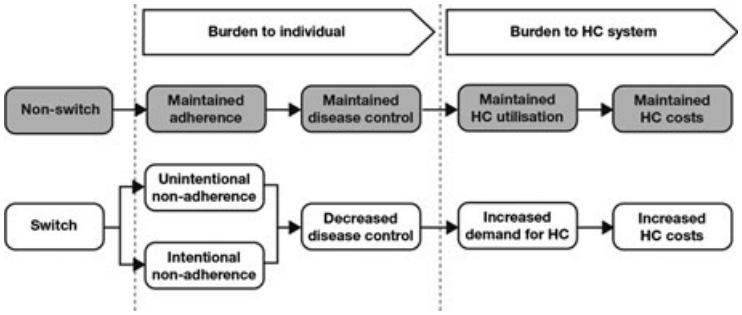

Figure 4 Potential clinical and economic consequences of switching well-controlled patients with asthma for cost reasons. HC, healthcare

The difference in costs of scheduled and unscheduled asthma healthcare visits in Europe was estimated by Williams et al. (44). Unscheduled visits accounted for almost one-half of the total asthma management healthcare expenditure (Figure 2B). Different patterns of unscheduled healthcare consumption were observed according to asthma severity. Among adults, 11% of patients reported at least one emergency room visit (ranging from 6% with mild intermittent symptoms to 17% with severe persistent symptoms). If unscheduled physician visits are considered, 24% of patients had at least one unscheduled visit (ranging from 15% to 38%, depending on disease severity).

In other chronic diseases, FDC therapies have been shown to improve adherence compared with individual monocomponents, thereby improving disease control (45,46); this is also thought to be applicable in asthma (32,33,47). In Sweden, combination budesonide (BUD)/formoterol (FM) inhalers were significantly more cost-effective than using separate BUD and FM inhalers (33). The cost of study medication was lower for the FDC BUD/FM inhaler than for separate BUD and FM [7822 Swedish krona (SEK) per year vs. 8530 SEK per year, respectively], and direct and indirect medical costs associated with treatment were considerably lower for the combination-inhaler group compared with separate-inhaler group (Figure 3).

Conclusion

The causal chain of events discussed above, and outlined in Figure 4, provides us with an opportunity to understand the complexity of possible negative outcomes associated with switching asthma medications and inhaler devices, driven by non-patient-related factors, at individual and organisational levels. A patient who is uncomfortable with handling an inhaler is at greater risk of critical handling errors, which compromises asthma control. Worsened asthma symptoms and an increased need for additional consultations regarding device handling technique logically lead to increased demand for healthcare services. Subsequently, higher healthcare service consumption as a result of increases in physician hours and other healthcare resource allocation results in higher costs.

To conclude, given the continually increasing pressure for reduced costs and efficient allocation of limited healthcare resources, an additional investment in ensuring high medication adherence may lead to greater savings because of potentially decreased demand for healthcare services. In contrast, savings achieved in acquisition costs may result in a greater net loss because of increased healthcare consumption, caused by decreased asthma control.

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Author contributions

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References

1 GINA report, Global Strategy for Asthma Management and Prevention, 2011. www.ginasthma.org (accessed June 2012)

2 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2003; **58**: i1–94.

3 Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Care Respir J* 2009; **18**: 243–9.

4 Horne R, Price D, Cleland J et al. Can asthma control be improved by understanding the patient's perspective? *BMC Pulm Med* 2007; **7**: 8.

5 Doyle S, Lloyd A, Williams A et al. What happens to patients who have their asthma device switched without their consent? *Prim Care Respir J* 2010; **19**: 131–9.

6 Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001; **107**: 3–8.

7 Price D. The way forward: dry powder inhalers should only be switched with physician agreement and patient training. *Int J Clin Pract Suppl* 2005; **59**: 36–7.

8 Bender BG, Rand C. Medication non-adherence and asthma treatment cost. *Curr Opin Allergy Clin Immunol* 2004; **4**: 191–5.

9 Haughney J, Price D, Barnes NC et al. Choosing inhaler devices for people with asthma: current knowledge and outstanding research needs. *Respir Med* 2010; **104**: 1237–45.

10 Virchow JC, Crompton GK, Dal Negro R et al. Importance of inhaler devices in the management of airway disease. *Respir Med* 2008; **102**: 10–9.

11 Lavorini F, Magnan A, Dubus JC et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. *Respir Med* 2008; **102**: 593–604.

12 Thomas M, Williams AE. Are outcomes the same with all dry powder inhalers? *Int J Clin Pract Suppl* 2005; **59**: 33–5.

13 Cochrane MG, Bala MV, Downs KE et al. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest* 2000; **117**: 542–50.

14 Gustafsson P, Taylor A, Zanen P, Chrystyn H. Can patients use all dry powder inhalers equally well? *Int J Clin Pract Suppl* 2005; **59**: 13–8.

15 Schulte M, Osseiran K, Betz R et al. Handling of and preferences for available dry powder inhaler systems by patients with asthma and COPD. *J Aerosol Med Pulm Drug Deliv* 2008; **21**: 321–8.

16 Taylor AGP. Do all dry powder inhalers show the same pharmaceutical performance? *Int J Clin Pract Suppl* 2005; **59**: 7–12.

17 Chrystyn H. Do patients show the same level of adherence with all dry powder inhalers? *Int J Clin Pract Suppl* 2005; **59**: 19–25.

18 Yu AP, Guerin A, de Leon DP et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. *Respir Med* 2011; **105**: 1861–71.

19 Rootmensen GN, van Keimpema AR, Jansen HM, de Haan RJ. Predictors of incorrect inhalation technique in patients with asthma or COPD: a study using a validated videotaped scoring method. *J Aerosol Med Pulm Drug Deliv* 2010; **23**: 323–8.

20 Roberts NJ, Ghiassi R, Partridge MR. Health literacy in COPD. *Int J Chron Obstruct Pulmon Dis* 2008; **3**: 499–507.

21 DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; **160**: 2101–7.

22 Melani AS, Bonavia M, Cilenti V et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011; **105**: 930–8.

23 Cohen JL, Mann DM, Wisnivesky JP et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol* 2009; **103**: 325–31.

24 Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest* 2006; **130**: 65S–72S.

25 Small M, Anderson P, Vickers A et al. Importance of inhaler-device satisfaction in asthma treatment: real-world observations of physician-observed compliance and clinical/patient-reported outcomes. *Adv Ther* 2011; **28**: 202–12.

26 Small M, Vickers A, Anderson P, Kay S. The patient-physician partnership in asthma: real-world observations associated with clinical and patient-reported outcomes. *Adv Ther* 2010; **27**: 591–9.

27 Zhong N, Zheng J, Wen F et al. Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronic obstructive pulmonary disease. *Curr Med Res Opin* 2012; **28**: 257–65.

28 Perrin K, Williams M, Wijesinghe M et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting beta-agonist inhaler therapy in asthma. *J Allergy Clin Immunol* 2010; **126**: 505–10.

29 Stempel DA, Stoloff SW, Carranza Rosenzweig JR et al. Adherence to asthma controller medication regimens. *Respir Med* 2005; **99**: 1263–7.

30 Stoloff SW, Stempel DA, Meyer J et al. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004; **113**: 245–51.

31 Huchon G, Magnussen H, Chuchalin A et al. Lung function and asthma control with beclomethasone and formoterol in a single inhaler. *Respir Med* 2009; **103**: 41–9.

32 Rosenhall L, Elvstrand A, Tilling B et al. One-year safety and efficacy of budesonide/formoterol in a single inhaler (Symbicort Turbuhaler) for the treatment of asthma. *Respir Med* 2003; **97**: 702–8.

33 Rosenhall L, Borg S, Andersson F, Ericsson K. Budesonide/formoterol in a single inhaler (Symbicort) reduces healthcare costs compared with separate inhalers in the treatment of asthma over 12 months. *Int J Clin Pract* 2003; **57**: 662–7.

34 Angus R, Reagon R, Cheesbrough A. Short-acting beta 2-agonist and oral corticosteroid use in asthma patients prescribed either concurrent beclomethasone and long-acting beta 2-agonist or salmeterol/fluticasone propionate combination. *Int J Clin Pract* 2005; **59**: 156–62.

35 Booker R. Do patients think that dry powder inhalers can be used interchangeably? *Int J Clin Pract* 2005; **59**: 30–2.

36 Molimard M, Le Gros V. Impact of patient-related factors on asthma control. *J Asthma* 2008; **45**: 109–13.

37 Williams LK, Pladevall M, Xi H et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004; **114**: 1288–93.

38 Stern L, Berman J, Lumry W et al. Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data. *Ann Allergy Asthma Immunol* 2006; **97**: 402–8.

39 Suissa S, Ernst P, Benayoun S et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; **343**: 332–6.

40 Thomas M, Price D, Chrystyn H et al. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. *BMC Pulm Med* 2009; **9**: 1.

41 Accordini S, Bugiani M, Arossa W et al. Poor control increases the economic cost of asthma. A multicentre population-based study. *Int Arch Allergy Immunol* 2006; **141**: 189–98.

42 Hoskins G, McCowan C, Neville RG et al. Risk factors and costs associated with an asthma attack. *Thorax* 2000; **55**: 19–24.

43 Lane S, Molina J, Plusa T. An international observational prospective study to determine the cost of asthma exacerbations (COAX). *Respir Med* 2006; **100**: 434–50.

44 Williams AE, Lloyd AC, Watson L, Rabe KF. Cost of scheduled and unscheduled asthma management in seven European Union countries. *Eur Respir Rev* 2006; **15**: 4–9.

45 Pan F, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adherence to prescription medications. *J Gen Intern Med* 2008; **23**: 611–4.

46 Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. *Am J Health Syst Pharm* 2007; **64**: 1279–83.

47 Bruggenjurgen B, Ezzat N, Kardos P, Buhl R. Economic evaluation of BDP/formoterol fixed vs two single inhalers in asthma treatment. *Allergy* 2010; **65**: 1108–15.

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